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CONTENTS

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THE EFFECTS OF VITAMIN D AND GLUTEN-FREE DIET IN IDIOPATHIC STEATORRHOEA[1]

By J. R. NASSIM, P. D. SAVILLE, P. B. COOK, and LILY MULLIGAN

(From the Royal National Orthopaedic Hospital, London, and the Institute of Orthopaedics)

The treatment of coeliac disease in children has been revolutionized since the observation of Dicke (1950) that the condition improved when the flour of wheat and rye was excluded from the diet. It was also shown by Weijers and van de Kamer (1950) that on this régime faecal fat was reduced. These findings were confirmed by Anderson, Frazer, French, Gerrard, Sammons, and Smellie (1952) and by Sheldon and Lawson (1952). It was further shown that the harmful effects of the flour were due not to the starch but to the protein (gluten) fraction (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Dicke, Weijers, and van de Kamer, 1953), and that the gliadin fraction of the gluten was more potent at producing relapse than the glutenin fraction (van de Kamer, Weijers, and Dicke, 1953). Subsequently it has been suggested by van de Kamer and Weijers (1955) that glutamine bound in protein, but not as free amino acid, was the potent factor in gliadin that produced coeliac disease. These authors pointed out that gliadin contains an unusually high proportion of glutamine (43 per cent.), and that the degree of sensitivity of a patient to a protein is quantitatively proportional to the content of glutamine in that protein.

Coeliac disease and idiopathic steatorrhoea are phasic in their manifestations, but there is no evidence that the defect is ever cured spontaneously; thus Gerrard, Ross, Astley, French, and Smellie (1955), in a reassessment of 32 children and adolescents who previously had been diagnosed as suffering from coeliac disease, and had been receiving a normal diet containing wheat gluten, found that none of them was completely free from symptoms; 18 of these patients, when they kept to a strict gluten-free diet, improved and had no steatorrhoea (Gerrard, Ross, and Smellie, 1955). Reports on the effects of a gluten-free diet on adults with idiopathic steatorrhoea have hitherto been meagre. Anderson, Frazer, French, Hawkins, Ross, and Sammons (1954) studied 12 adults with iodiopathic steatorrhoea and seven with tropical sprue; the patients were kept on a wheat-free diet for not less than two months. They found that the fat balance in five of the patients with idiopathic steatorrhoea returned to normal, and in seven there was no significant change; and that in tropical sprue wheat gluten did not play a significant part. McIver (1952) reported the beneficial

[1] Received March 28, 1958.

effect of a gluten-free diet in a woman of 45 years, and Ruffin, Carter, Johnston, and Baylis (1954) reported striking improvement in a woman of 39 years, and stated that two further patients with the 'sprue syndrome' had also improved. Thus it would appear that in infants and children the response to a gluten-free diet is universally good, whereas only a proportion of adults may expect to be improved.

With regard to the calcium balance in steatorrhoea and the response to vitamin D, opinion is still not crystallized, and full balance data are few. Findlay and Sharpe (1919) carried out a balance study in a woman of 52 years, who had suffered from coeliac disease since infancy and had chronic tetany. She was given a special diet, and faecal collections were made in her own home. These studies demonstrated poor absorption of both fat and calcium. Barach and Murray (1920), studying a case of sprue with tetany, felt that the calcium absorption was insufficient because the calcium was incorporated in combination with the fats. Linder and Harris (1929) conducted metabolic studies in three women with tetany and fatty diarrhoea, and concluded that the poor calcium absorption was due to lack of vitamin D and could be corrected by adequate dosage of ergosterol and fat restriction. They did not think that the soap content of the stools was sufficient to account for the poor absorption. Bauer and Marble (1932), in a study of a case of osteomalacia, found that the faulty absorption of calcium and phosphorus was due to vitamin-D deficiency and seemed to bear no relation to the fat output, though it was conceivable that most of the vitamin D was excreted with the excess of fat. Bassett, Keutmann, Hyde, Van Alstine, and Russ (1939), and Bassett, Hyde, Keutmann, and Van Alstine (1939) carried out metabolic studies of four patients, whose diets were varied with regard to the starch and fat content. They noticed that high dosage of vitamin D improved the absorption of both calcium and phosphorus, that an increase of dietary fat increased the loss of calcium in the faeces, and that a reduction of calcium intake facilitated absorption of fatty acids. Fourman and Spray (1948) studied a woman of 60 years with steatorrhoea and osteomalacia, and found that she did not improve with supplements of calcium and 12,000 i.u. of vitamin D, but positive balance was achieved when the vitamin was given intramuscularly. From this evidence they inferred a failure to absorb vitamin D. Badenoch and Fourman (1954) reported six patients with osteomalacia and steatorrhoea, in two of whom balance studies were carried out. They came to the conclusion that there was a failure to absorb vitamin D, that there might also be a failure to absorb calcium because of the formation of soaps, and that this defect could be overcome by giving the vitamin parenterally or in large doses by mouth.

The present paper concerns metabolic studies conducted in an attempt to provide further information concerning the actions of vitamin D and its relationship to gluten. Evidence is presented to support the theory that secondary hyperparathyroidism may play an important part in the regulation of calcium absorption in the disease.

Patients Investigated

A consecutive series of patients (two male and seven female) suffering from steatorrhoea has been studied. Their ages ranged from eight to 60 years (Tables I and II). While it is true that an increasing fat intake produces a small increment in faecal fat (Wollaeger, Comfort, and Osterberg, 1947), for all practical

TABLE I

Summary of Clinical Findings

Case number	*Sex*	*Age (years)*	*Bowel symptoms*	*Sore tongue*	*Clubbing of fingers*	*Stature*	*Remarks*
1	F	38	Episodic diarrhoea. Pale stools	0	0	Stunted	Rickets as a child. Bilateral femoral osteotomies
2	M	49	Frequent, offensive, bulky stools	+	0	Normal	..
3	F	18	Always bulky stools, twice each day	+	0	Normal	..
4	M	8	Pale, offensive, bulky stools	0	0	Normal	..
5	F	21	Offensive stools	+	Slight	Dwarfed	Infantilism. Pigmentation of face. Diagnosed as coeliac disease at age of 2 years
6	F	15	Loose, pale, bulky stools	+	Slight	Normal	..
7	F	56	Recurrent diarrhoea	+	0	Recent loss of height	Diminution in height of 12 in. in previous 18 months, with loss of weight (2 stone)
8	F	60	Normal	+	0	Kyphoscoliosis	Severe bone pain. Menses always scanty
9	F	57	Two or three loose, pale motions per day	0	0	Stunted	Severe bone pain and tenderness. Emaciated. Unable to get up unaided

purposes a daily faecal fat excretion exceeding 5 g. is abnormal (Frazer, 1955). This criterion of diagnosis has been adopted throughout. The glucose-tolerance curve was flattened in every case. Anaemia was noted in some patients, and was not related to the presence of bone disease; thus the multiple deficiencies that arise in steatorrhoea may be manifested independently of each other.

Methods

All patients were admitted to the Metabolic Unit of the Royal National Orthopaedic Hospital. They were not confined to bed. In order to reduce the tedium of the diet, three daily menus were prepared and given in constant order of rotation. All food was weighed, and the calculated daily values for calcium, phosphorus, nitrogen, and fat were made virtually identical in the three menus. The food was prepared by the dietician in the Metabolic Unit kitchen. Bulk

supplies of meat, biscuits, and homogenized milk were used. Bread was made in the Unit from unfortified flour, while gluten-free bread was made from gluten-free flour obtained from the Energen Bread Company Ltd. Distilled water was used throughout. The diets were analysed for calcium, phosphorus, nitrogen, and fat on several occasions throughout the studies and, where discrepancies arose between calculated and analysed constituents, the analysed results were taken. Stools and urine were collected in six-day periods. Urine was preserved by adding 1 per cent. concentrated hydrochloric acid. Faecal collections were

TABLE II

Summary of Laboratory Investigations

Case number	*Haemoglobin (100% = 14·8 g./100 ml.)*	*Type of anaemia*	*Glucose-tolerance curve*	*Plasma albumin (g./100 ml.)*	*Plasma globulin (g./100 ml.)*	*Serum calcium (mg./100 ml.)*	*Alkaline phosphatase (King–Armstrong units)*	*Blood urea (mg./100 ml.)*	*Radiography*
1	103	..	Flattened	4·6	2·0	10·3	30	..	Demineralization. Pseudo-fractures in feet, ribs, left hip, and axillary borders of scapulae
2	66	Mixed	Flattened	3·5	1·8	8·2	6	20	Normal
3	62	Hypochromic	Flattened	4·5	2·7	9·3	9	19	Normal
4	59	Mixed	Flattened	..	..	9·3	37	14	Active rickets
5	54	Mixed	Flattened	4·4	2·7	6·2	68	11	Demineralization. Skeletal age equivalent to 10 yrs. Pseudo-fractures of ulnae and metatarsals of both feet. Hyperparathyroidism (subperiosteal erosions of phalanges and ischiopubic rami)
6	64	Macrocytic	Flattened	3·8	2·1	8·8	46	13	Demineralization. Hyperparathyroidism (notching of iliac crests and 'fluffiness' of upper borders of femoral necks)
7	102	..	Flattened	3·7	2·1	8·1	45	12	Gross demineralization. Pseudo-fractures of clavicles, ribs, ulnae, tibiae, fibulae, pelvis, hands, feet
8	80	Mixed	Flattened	4·5	2·6	9·0	36	14	Demineralization
9	70	Mixed	Flattened	4·0	2·6	8·5	28	21	Gross demineralization. Pseudo-fractures in all long bones

demarcated by the administration of 0·5 g. of carmine. The three daily menus were homogenized separately in a Waring blendor after addition of sufficient water. Six-day faecal collections were homogenized in the same way. The total weight of the homogenate was determined, and weighed samples were dried and then ashed for calcium and phosphorus determination. Fat and nitrogen were estimated in a weighed portion of wet homogenate. Throughout the studies the calcium in food, faeces, and urine was estimated by the method of Clark and Collip (1925), phosphorus by the method of Briggs (1922), and nitrogen by the method of Koch and McMeekin (1924). Serum inorganic phosphorus and

alkaline phosphatase were estimated by the method of King (1947). Faecal fat was estimated by a modification of King's method. Blood for analysis was always taken immediately before lunch, on the same day of each week.

Metabolic Studies (Figs. 1 to 9)

Metabolic data are charted according to the method of Reifenstein, Albright, and Wells (1945). Dietary intake is plotted downwards from the base-line. Output is recorded in blocks built upon the intake line towards the base-line. The lower of the two blocks represents faecal excretion, and the upper urinary excretion. Thus a gap between the base-line and the blocks represents a positive balance, and conversely, if the blocks are above the base-line, a negative balance is represented. Attempts were made to keep dietary intake constant, but this was not always possible, and alterations are clearly represented. Each value plotted represents the daily average computed from a six-day collection. Faecal fat (g. per day) appears as a block against a vertical scale. Occasionally it was not possible to differentiate single six-day faecal collections with certainty. At such times the average for a longer period was calculated, and is shown on the diagram by absence of dividing lines (for example, in periods 22 and 23 in Case 2). For brevity, many of the salient clinical features and results of investigations have been summarized in Tables I and II. In the following pages a brief clinical note appears for each of the nine patients, and is followed by comments upon the metabolic data.

Case 1. A housewife aged 38 years had always been undersized (height 4 ft. 7 in.) and in poor health. She had rickets as a child, and had bilateral femoral osteotomies to correct bone deformity. Three years before admission she had severe pain in her hips, back, shoulders, and feet. At the time of admission she was unable to walk. Her appetite was capricious, and episodic diarrhoea with pale stools had been present throughout her life. Menstruation was scanty and completely irregular. Treatment had been given for the previous two years at another hospital for anaemia and 'rheumatism'. Frequency of micturition and dysuria had been present for six months. She had not worked for one year owing to her incapacitating symptoms. There was radiographic evidence of osteomalacia.

Notes on metabolic data. The fat-intake was 81 g. per day. *Periods 1 and 2*: (normal diet.) Note the high concentration of faecal fat, but positive balance for calcium. Urinary calcium was nil. *Periods 3 to 5*: on a gluten-free diet the faecal calcium was immediately halved, but the decrease in faecal fat was slight. Nitrogen balance was positive. There was a sharp increase in serum inorganic phosphorus. *Periods 6 to 8*: with a return to normal diet there was an increase in faecal fat after one period, and a negative nitrogen balance. A slight increase occurred in faecal calcium.

Progress. The patient responded well to calciferol in large doses (15 mg. per day orally), with healing of the pseudo-fractures. After leaving hospital she had an episode of abdominal discomfort with diarrhoea, and decided to take 'energen' rolls (starch-free gluten), which aggravated her condition. She was readmitted, and responded to a gluten-free diet. It was noted that the patient was unreliable and unlikely to adhere to any dietary régime. Her condition,

however, has continued to be much better than before she began treatment. Periodic radiography has not demonstrated any further pseudo-fractures. Apart from occasional back pain she has remained free from symptoms.

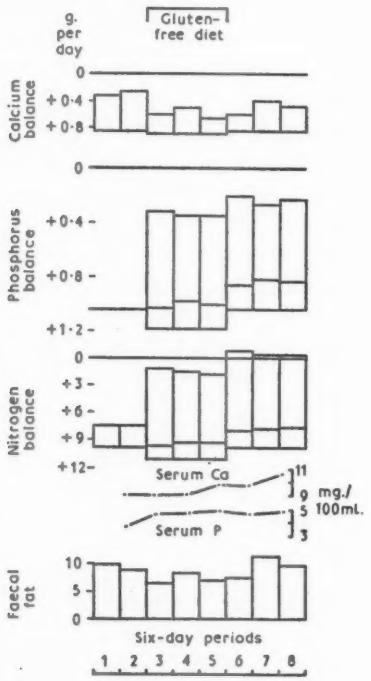

FIG. 1. Case 1.

Case 2. A Civil Servant aged 49 years had enjoyed good health until six months before admission, when he lost weight. He had lost over two stone in three months. Appetite was poor, and he developed a swollen, ulcerated tongue. He vomited once a day, and passed frequent, offensive, bulky stools. Previously his bowel habit had been normal. In addition to the investigations summarized in the Tables, a barium meal was normal, and examination for occult blood negative.

Notes on metabolic data. The fat-intake was 90 g. per day. *Periods 1 to 3*: calcium balance was negative, the faecal calcium exceeding the intake. Phosphorus balance was maintained, and there was a positive nitrogen balance. Faecal fat was 19 g. per day. *Periods 4 to 10*: gluten-free diet produced very slight diminution in faecal fat. Addition of calciferol, 0·25 mg. daily, by mouth, reduced faecal calcium, with an increase in urinary calcium and improved fat-absorption. Note the slight increase in serum inorganic phosphorus. *Periods 11 to 16*: on a low-fat diet (35 g. per day) with gluten, the faecal fat was much reduced, but remained above 7 g. per day, while faecal calcium approximated to the intake. Note that at this stage oral calciferol, 0·25 mg. daily, no longer had an effect on faecal or urinary calcium. In the presence of gluten the patient had become insensitive to calciferol.

At this point the patient left hospital, taking a low-fat diet containing gluten. He had gained weight, the stools had become normal, and the haemoglobin rose to 94 per cent. (14 g. per 100 ml.). As an out-patient he began to deteriorate slightly, and a gluten-free diet was initiated. After six months he claimed to be feeling in perfect health, and was readmitted for further study.

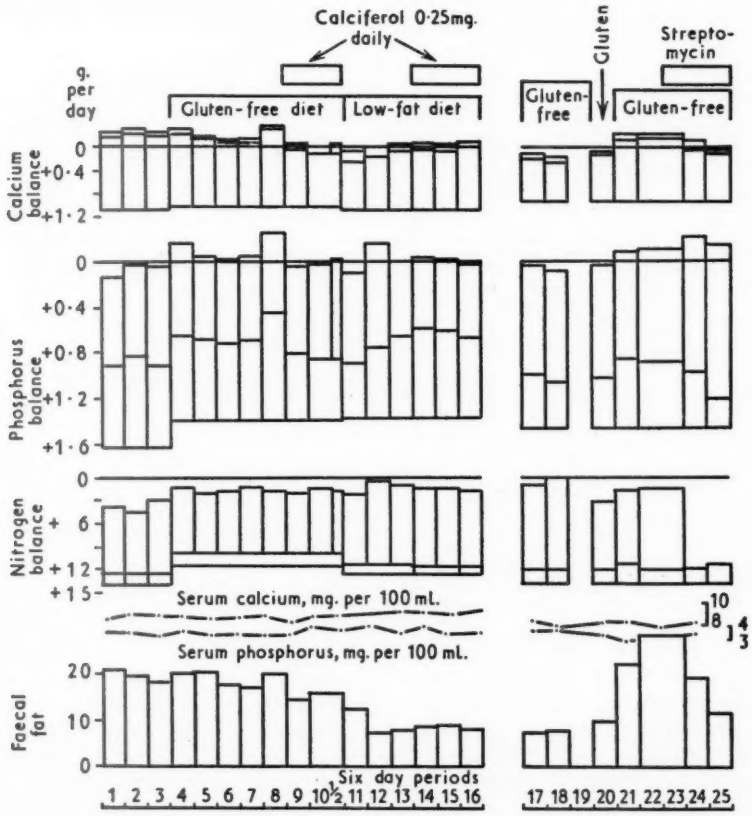

FIG. 2. Case 2.

Periods 17 and 18: with an intake of 80 g. fat per day, 7 to 8 g. appeared in the faeces. Calcium, phosphorus, and nitrogen balances were positive. *Period 20*: on a normal diet the patient relapsed after three days, and felt too ill to continue it, although the adverse effect on the balance at this stage was slight. *Periods 21 and 22*: in spite of a return to a gluten-free diet there was a continued increase in faecal fat, which reached 28 g. per day. Faecal calcium increased to exceed the intake, and the phosphorus balance also became negative. *Periods 23 to 25*: the patient was receiving oral streptomycin and continuing a gluten-free diet. There was a rapid step-like decrease in faecal calcium, phosphorus, and fat, commensurate with the previous increase during relapse.

Progress. Steady improvement has followed withdrawal of gluten from the diet. When last seen the patient claimed to be in perfect health.

Case 3. A girl of 18 years had complained of mouth ulcers and recurrent abdominal pain since the age of 10 years. Anaemia had been present for several years, and had proved resistant to treatment. The stools had always been bulky, with two motions per day. They were often pale when abdominal pain was present. Three siblings all enjoyed good health. Examination revealed an adequately nourished girl of normal stature (5 ft. 4 in.), with no abnormal physical signs. An attempt was made to treat the anaemia with intravenous iron, without success.

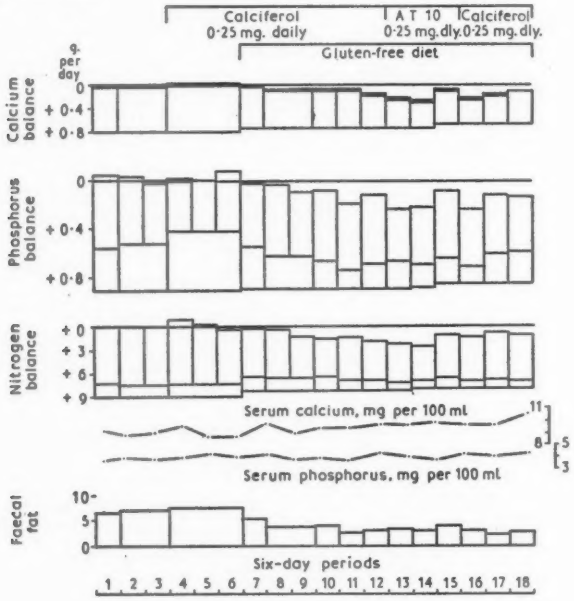

FIG. 3. Case 3.

Notes on metabolic data. The fat-intake was 44 g. per day. *Periods 1 to 3*: faecal fat was increased. Faecal calcium was equal to the intake, and urine calcium nil, producing a zero calcium balance. Phosphorus balance was slightly negative, and nitrogen balance was maintained. *Periods 4 to 6*: the patient was quite insensitive to calciferol: 0·25 mg. daily by mouth had virtually no metabolic effect. *Periods 7 to 18*: gluten-free diet reduced faecal fat to normal levels. Notice the immediate sensitization to calciferol, shown by step-like decrease in faecal calcium, causing an increasingly positive balance. This trend was continued when dihydrotachysterol (AT10) was substituted in equivalent dosage. The very low level of urine calcium throughout suggests continuing calcium deficiency despite lack of overt osteomalacia, either chemical or radiological.

Progress. The patient was still anaemic after completion of the balance studies. She was discharged, taking a gluten-free diet with oral iron. The haemoglobin rose from 62 per cent. to 96 per cent. in two months, and was maintained at this level without iron supplements. The patient's weight has increased, and her relatives have been impressed by the improvement in her personality and by her increased vitality.

Case 4. A Eurasion boy of eight years was admitted to hospital with knock-

knees. Since the age of 12 months he had passed pale, offensive, bulky stools. He had always been troubled by nocturnal enuresis, partially controlled by restricting his fluid intake. Radiography showed active rickets.

Notes on metabolic data. The fat-intake was 84 g. per day, and nitrogen 9·12 g. per day. *Periods 1 to 3*: on a normal diet the faecal levels of fat and nitrogen were high. The patient was in balance for calcium, with the faecal calcium equal to the intake. Urine calcium was absent. The serum calcium and

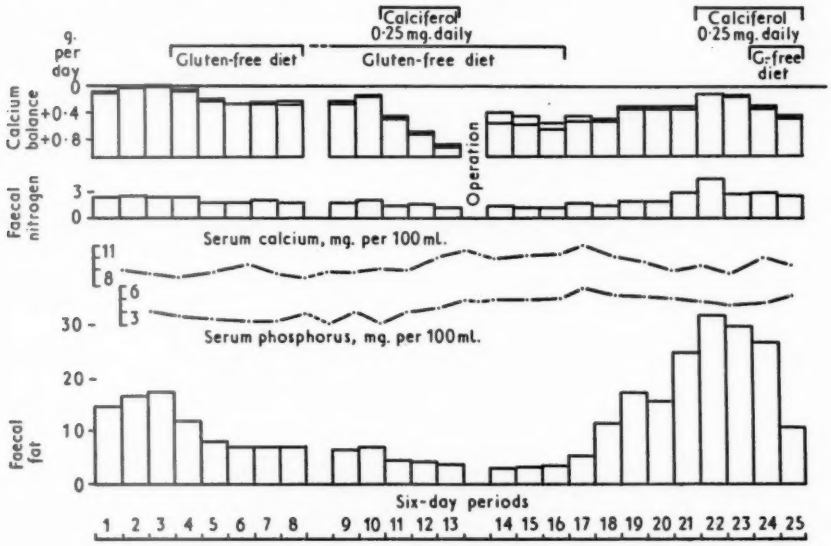

FIG. 4. Case 4.

inorganic phosphorus levels were low. *Periods 4 to 16*: on a gluten-free diet there was progressive diminution of faecal fat, with a concomitant reduction of faecal calcium. In periods 11 to 13, 0·25 mg. of calciferol daily, given orally, caused a step-like decrease in faecal calcium, which was associated with a further decrease in faecal fat. There was a simultaneous increase in serum inorganic phosphorus from 3 mg. to 5 mg. per 100 ml. This increase continued until the gluten-free diet was discontinued (period 17). There was also a slight increase in serum calcium. Between periods 13 and 14 the patient had an operation for genu valgum. Note the high concentration of urine calcium in period 14 despite the continued positive calcium balance. This increase occurred during immobilization in plaster, and decreased thereafter. *Periods 17 to 23*: on a normal diet there was a progressive increase in faecal fat, far in excess of the original levels. At the same time faecal calcium increased only slightly. The urine calcium level fell to nil. *Periods 22 and 23*: the patient was no longer sensitive to calciferol, 0·25 mg. daily, given orally. *Periods 24 and 25*: on a gluten-free diet the faecal fat decreased, but was still grossly abnormal. The patient was now sensitive to oral calciferol, 0·25 mg. daily, which produced a decrease in faecal calcium.

Progress. The gluten-free diet with calciferol healed the rickets. The patient has remained free of symptoms, and gained seven inches in height in 18 months. Nocturnal enuresis ceased soon after a gluten-free diet was begun.

Case 5. A woman of 21 years. Offensive stools and vomiting attacks had led to a diagnosis of coeliac disease at the age of two years. Her appetite had always been capricious. She had never menstruated. She had suffered bone pain for two years, mainly in the feet, ribs, and arms. Frequent mouth ulcers and sore tongue were other complaints. She had nine siblings, all of whom were well.

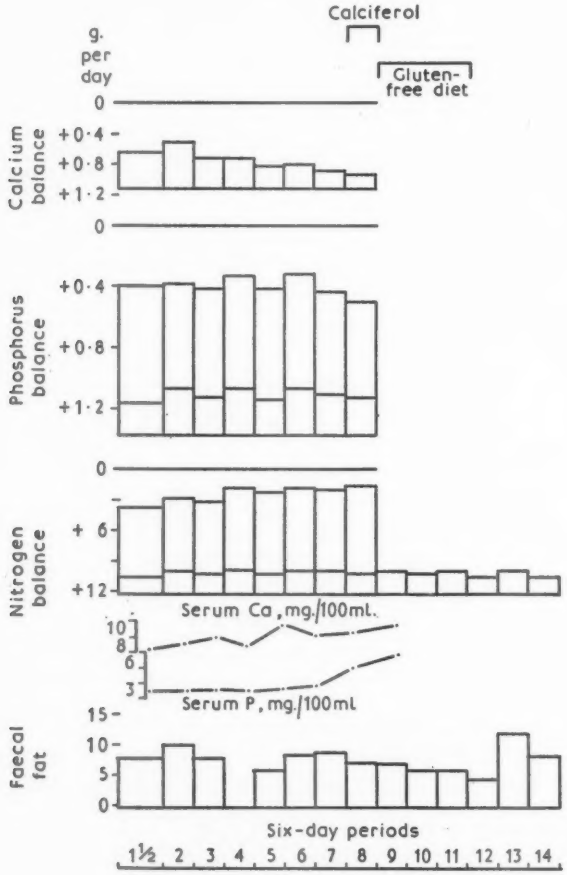

FIG. 5. Case 5.

Examination revealed a dwarfed, pale, infantile woman, with no secondary sexual characteristics. Her appearance suggested an age of 10 years rather than 21. There was brown pigmentation of the face of 'butterfly' distribution, and minimal clubbing of the fingers. The bones of the forearms and feet were tender. The lower costal margins were bulging and wide. The mucous membranes were pale, and she had ulcers in the mouth. The abdomen was distended and tympanitic. Her height was 4 ft. 5½ in., and weight 62 lb. Urinary 17-ketosteroid excretion was 4·7 mg. in 24 hours. Large doses of B vitamins (including nicotinamide) had been given. Radiography revealed osteomalacia and hyperparathyroidism.

Notes on metabolic data. The fat-intake was 41 g. per day. *Periods 1 to 7*: on a normal diet faecal fat was increased. Calcium, phosphorus, and nitrogen balances were strongly positive. Urinary calcium was absent; the faecal calcium level tended to drop continuously, the serum calcium increasing *pari passu* with the increasingly positive calcium balance. *Period 8*: a further slight decrease in faecal calcium, but a sharp rise in the level of serum inorganic phosphorus, followed administration of calciferol, 5 mg. daily. *Periods 9 to 11*: gluten-free diet produced a very small improvement in faecal fat excretion. *Periods 12 to 14*: a return to normal diet produced an increase of faecal fat exceeding the original levels.

Progress. Clinical improvement with a gluten-free diet, supplemented with intravenous iron, oral folic acid, and vitamin B, was remarkable. The pseudo-fractures had healed before the patient left hospital. Hyperparathyroid changes have regressed completely, and the pellagrous pigmentation has faded. A steady increase in weight (two stone in the first six months) has been associated with an increase in height of four and a half inches. After nine months the breasts began to develop, and pubic and axillary hair appeared. The patient has commenced to menstruate, and her psychological condition is much improved. She has continued her gluten-free diet, without supplements, as an out-patient.

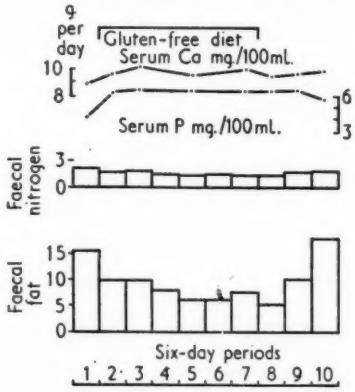

FIG. 6. Case 6.

Case 6. A girl of 15 years had suffered abdominal discomfort and had passed loose, pale, bulky stools since infancy. Her growth was stunted (height 4 ft. 7 in.); she often had a sore tongue, and respiratory infections were frequent. Six years before admission she had a fractured metatarsal, apparently spontaneous. Radiographs revealed secondary hyperparathyroidism.

Notes on metabolic data. The fat-intake was 60 g. per day, and nitrogen 10·5 g. per day. *Period 1*: faecal fat was 15 g. per day. *Periods 2 to 7*: gluten-free diet produced a rapid decrease in faecal fat and a lower level of faecal nitrogen. *Periods 8 to 10*: a normal diet, after an initial slight decrease in faecal fat, produced a relapse. In periods 9 and 10 the faecal fat exceeded the amount excreted in period 1. Note the rise in serum inorganic phosphorus to almost hypoparathyroid levels, about 6·3 mg. per 100 ml., on a gluten-free diet.

Progress. With a gluten-free diet the patient gained weight (one and a half stone in six months) and height, and was much improved. Supplements of

intravenous iron and vitamin D were given, and the haemoglobin increased to 104 per cent. in two months. Her entire demeanour altered, and menstruation began. She has continued to lead a full life as a healthy adolescent since leaving hospital.

Case 7. A housewife of 56 years had passed pale, bulky, offensive stools for as long as she could remember, with recurrent diarrhoea, and frequent mouth

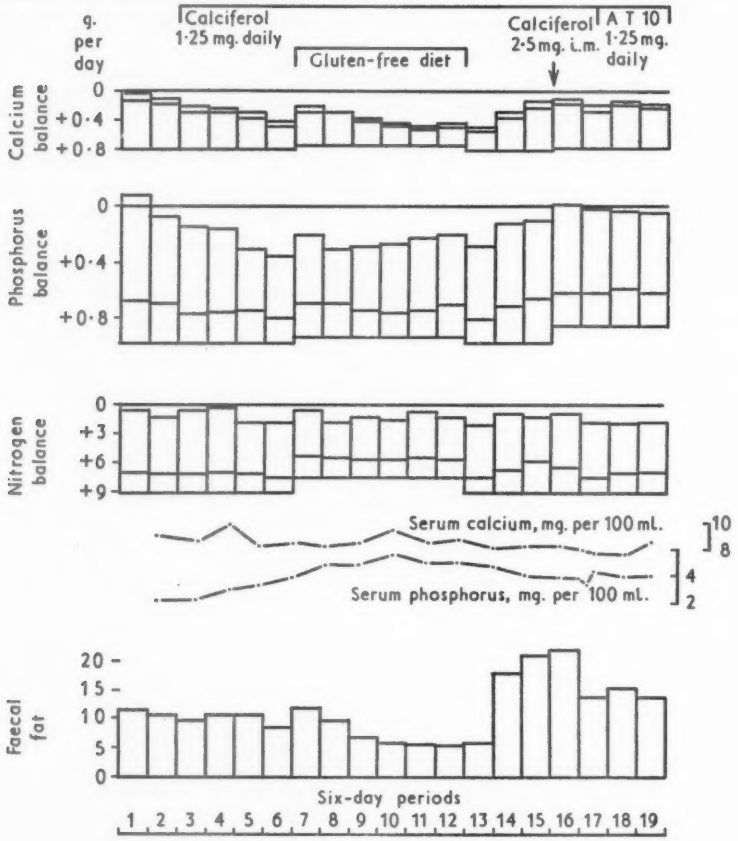

FIG. 7. Case. 7.

ulcers and soreness of the tongue. She had been diagnosed as suffering from the sprue syndrome in 1952, when her anaemia was treated with liver injections and folic acid. For two years she had noticed progressive difficulty in walking, and was now confined to bed. Her height had diminished by 12 inches in the previous 18 months, and there had been a loss of two stone in weight. Examination revealed a frail woman, looking older than her years, with gross kyphoscoliosis and chest deformity. Bone biopsy and radiography revealed osteomalacia.

Notes on metabolic data. The fat-intake was 50 g. per day. *Periods 1 and 2*: on a normal diet faecal fat was increased; calcium balance was maintained. Note the normal urinary excretion of calcium in spite of osteomalacia. The level

of serum inorganic phosphorus was very low. *Periods 3 to 6*: calciferol, 1·25 mg. daily by mouth, caused a progressive decrease in faecal calcium. Urinary calcium decreased, with a sharp decrease in urinary phosphorus and a steady rise in the level of serum inorganic phosphorus. *Periods 7 to 12*: gluten-free diet caused a decrease of faecal fat; the levels of urinary and faecal calcium continued to fall with increasing sensitivity to vitamin D. *Periods 13 to 19*: on a normal diet a violent relapse occurred in faecal fat excretion, to double the previous levels. At the same time the patient lost sensitivity to calciferol, and urinary calcium again increased, as well as faecal calcium, although the patient was still in slightly positive balance. Intramuscular calciferol 2·5 mg., in addition to the oral calciferol, had no effect. Dihydrotachysterol (AT10) by mouth, substituted for calciferol in periods 17 to 19, likewise had no metabolic effect.

Progress. Response to treatment with a gluten-free diet, supplemented with vitamin D, was excellent. This treatment was continued after completion of the balance studies, and has resulted in healing of the fractures. The patient was able to walk about again, and she continues to improve.

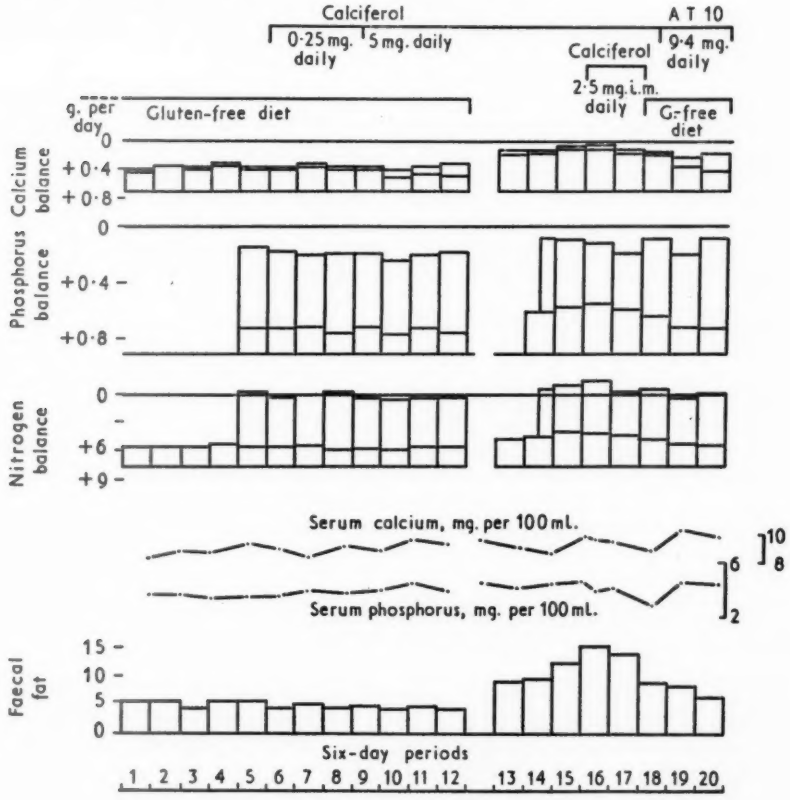

FIG. 8. Case 8.

Case 8. A woman of 60 years had been treated for 16 years for recurrent anaemia. Nine years before admission she had been diagnosed as suffering from

the Plummer–Vinson syndrome when she had an iron-deficiency anaemia (haemoglobin 40 per cent.) coupled with dysphagia. This condition responded to oral iron, thyroid, and multivitamin therapy (including cyanocobalamin). Three years before the present investigation she developed bone pain, which became increasingly severe, with progressive kyphoscoliosis. She was found to be anaemic again, with macrocytosis. Sternal-marrow and lymph-node biopsies gave no diagnostic information. The patient was given a course of radiotherapy to the spine, without symptomatic improvement. Finally fat-balance studies showed her to be suffering from steatorrhoea. Her bowels always moved once or twice a day, but she had no diarrhoea until two weeks before the present admission. Menses had always been scanty. At the time of her admission she was complaining of pain in the back, hands, feet, shins, and hips. She had pain in the chest on coughing, and there had been recent cramps in the hands and feet. She had been unable to work for the previous year because of her symptoms. For the two weeks preceding her transfer to the Royal National Orthopaedic Hospital she had been receiving a gluten-free diet, with oral calciferol 0·5 mg. per day. Examination revealed a thin, pale, elderly woman, with severe kyphoscoliosis and a protuberant abdomen. There was no axillary hair, and little pubic hair. Bone biopsy from the iliac crest showed wide osteoid seams diagnostic of osteomalacia.

Notes on metabolic data. The patient had been treated with a gluten-free diet for two weeks before balance studies were commenced. The fat-intake during the study was 50 g. per day. *Periods 1 to 5*: faecal fat excretion was virtually normal; there was a strongly positive calcium balance, due to a low level of faecal calcium and a very low level of urine calcium. *Periods 6 to 8*: calciferol, 0·25 mg. daily by mouth, had virtually no effect, except a slight increase in urine calcium. *Periods 9 to 12*: 5 mg. of oral calciferol daily merely altered the partition between urinary and faecal calcium, but the nitrogen balance became positive, and there was a slight decrease in faecal fat, commensurate with the decrease in faecal calcium. Twelve days of normal diet followed, during which no balance studies were made. *Periods 13 to 20*: note the marked increase in faecal fat, and concomitant increase in faecal phosphorus and nitrogen. The calciferol effect had disappeared, and there was an increase in faecal calcium and decrease in urine calcium, which continued in spite of parenteral calciferol (2·5 mg. daily) until a gluten-free diet was recommenced at period 18. With parenteral calciferol there was a steep drop in the level of serum inorganic phosphorus. In periods 18 to 20 gluten-free diet immediately sensitized the patient once more to the calciferol-like effect of dihydrotachysterol (AT10), which, however, was given in slightly larger doses. Faecal fat was decreased, but not yet to normal levels.

Progress. The patient was considerably improved when she left hospital, and this improvement has been maintained for several months.

Case 9. A woman of 57 years complained of a tendency to bouts of diarrhoea, which had been present all her life; she habitually passed two or three loose, pale motions each day. For the four years preceding her admission to hospital she experienced increasingly severe pain, which she said seemed to be in every bone in her body. Eighteen months before admission she sustained a fracture of the left tibia from a trivial injury, and since then she had worn a caliper and could only get about on crutches. In recent months she had been entirely bedridden because of pain. For the past 15 years she had been treated for anaemia, and had had injections of liver extract for the whole of that time. All her life

she had suffered from winter bronchitis, and tended to get mild attacks of bronchial asthma. At the age of eight years she had had Bright's disease, but could not remember any details of the illness.

Examination revealed a stunted, emaciated woman, who looked older than her years. Her height was 4 ft. 6 in. She was unable to rise from the lying position unaided, mainly because of bone pain. The chest was barrel-shaped, and scattered rhonchi were heard over both lungs. There was tenderness over the bones of all four limbs, and bowing of the clavicles which seemed to result from the use of crutches. Radiographs showed osteomalacia.

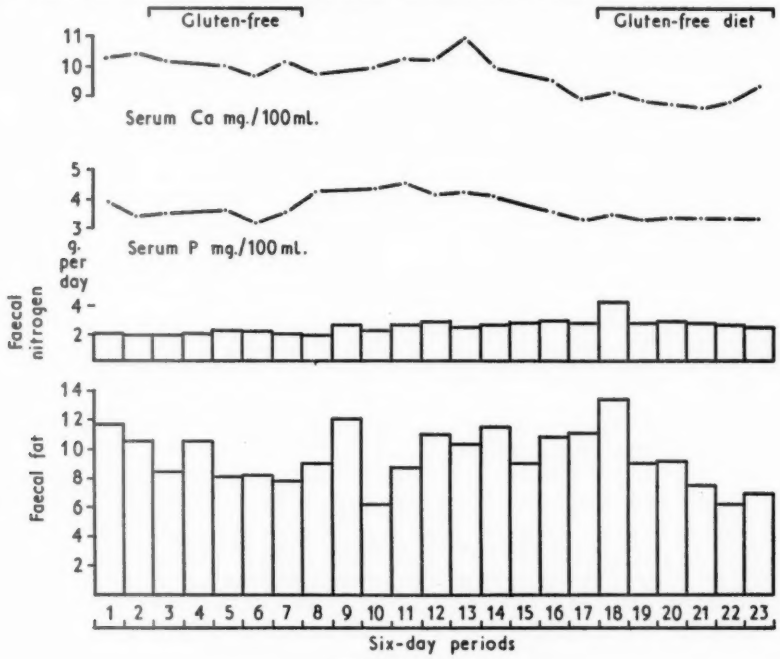

FIG. 9. Case 9.

Initial progress. The patient was given multivitamin therapy, with intravenous iron, and the haemoglobin level rose rapidly to 100 per cent. (14·8 g. per 100 ml.). In addition she received a low-fat diet, a high calcium intake, and 2·5 mg. of calciferol by mouth daily, with a weekly supplement of 2·5 mg. of calciferol given intramuscularly. In eight weeks the serum inorganic phosphorus increased from 2·8 mg. to 4·9 mg. per 100 ml., bone pain resolved, and at the same time radiological healing of pseudo-fractures could be discerned. The patient was sent home, taking 3·75 mg. of calciferol daily, which she continued for the next four months. She felt much better than she had for years, but still had occasional bone pain. The serum calcium had reached 10·5 mg. per 100 ml. In the next six months 15 mg. of calciferol was given daily, but the serum calcium remained between 9 mg. and 10 mg. per 100 ml., while the serum inorganic phosphorus was approximately 4·8 mg. per 100 ml. There was, however, a recurrence of pale, bulky stools, and of backache, and the patient developed cheilosis. She was readmitted for balance studies and a trial of gluten-free diet.

Notes on metabolic data. The fat-intake was 70 g. per day, and nitrogen 9·06 g.

per day. *Periods 1 and 2*: the faecal fat was about 10 g. per day. *Periods 3 to 7*: gluten-free diet produced a small but probably significant reduction in faecal fat, to about 8 g. per day. *Periods 8 and 9*: reversion to a diet containing gluten resulted in a step-like increase in faecal fat and nitrogen, in excess of the original levels. *Periods 10 to 17*: 0·5 g. of oxytetracycline was given daily for three days, and faecal fat was reduced by nearly a half, but this improvement was followed by a further step-like increase in fat and nitrogen. This increase persisted at a level similar to that seen in period 9, except for a less marked improvement following a second three-day course of the same antibiotic (period 15). *Periods 18 to 23*: a return to gluten-free diet supplemented, in period 19 only, by phthalylsulphathiazole (8 g. per day orally) and streptomycin (2 g. per day orally) resulted in an initial increase in faecal fat, while faecal nitrogen was doubled to nearly 4 g. per day. Thereafter the levels of faecal fat and nitrogen fell, the final levels of fat being below those observed in the control period.

Subsequent progress. The institution of a gluten-free diet was followed by a slow and moderate improvement in the patient's clinical state, but this change was by no means striking. Shortly after starting the diet the serum calcium rose to 11·2 mg. per 100 ml., although the patient was now taking only 2·5 mg. of calciferol daily.

Summary of Results

1. In every case clinical improvement followed the introduction of a gluten-free diet.

2. The discontinuation of a gluten-free diet was usually followed by a violent clinical and biochemical relapse.

TABLE III

Serum Inorganic Phosphorus (mg./100 ml.)

A: lowest readings before treatment of any kind.
B: highest readings after treatment with gluten-free diet or calciferol, or both.

Case number	A	B
1	2·0	4·8
2	3·4	3·5
3	3·9	4·3
4	3·2	5·1
5	2·0	6·0
6	3·5	6·3
7	2·2	5·5
8	..	5·0
9	2·8	4·9

3. The patients appeared to be very resistant to the action of vitamin D given orally or parenterally. There was evidence of increased sensitivity to the action of vitamin D when it was accompanied by a gluten-free diet, irrespective of the state of fat-absorption.

4. The level of serum inorganic phosphorus tended to be low before treatment, and six patients showed a definite increase in serum inorganic phosphorus after treatment with gluten-free diet or vitamin D (Cases 1, 4, 5, 6, 7, and 9) (Table III).

5. The calcium balance was studied in seven patients. Four (Cases 1, 4, 5, and 7) were in positive balance before treatment of any kind was begun. The calcium balance seemed to bear no relation to the degree of steatorrhoea.

6. Osteomalacia (pseudo-fractures or active rickets) was present in five patients (Cases 1, 4, 5, 7, and 9). Three of these patients had strongly positive calcium balances.

7. A negative calcium balance was present in one patient (Case 2) without evidence of osteomalacia.

Discussion

The role of gluten. There have been several reports in recent years of the treatment of idiopathic steatorrhoea with a gluten-free diet (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Ruffin, Carter, Johnston, and Baylis, 1954; Sheldon and Lawson, 1952). Recently French, Hawkins, and Smith (1957) reported prolonged studies of faecal fat in 22 patients suffering from idiopathic steatorrhoea. In 16 cases faecal fat reverted to normal on a gluten-free diet, but six patients failed to respond. No chemical or clinical features distinguished those patients who responded to gluten-free diet from those who did not. Our results are similar. In six patients (Cases 3, 4, 5, 6, 7, and 8), faecal fat reverted to normal, but in the other three it did not. Two points of interest must be stressed. First, it is often possible to demonstrate an altered reaction to the effects of vitamin D when gluten is excluded from the diet. Secondly, the improvement in fat-absorption on a gluten-free diet is often slow, and may be incomplete. Reversion to a normal diet, however, caused rapid relapse, usually to a degree worse than before treatment was started, and often accompanied by severe clinical symptoms. This observation has proved useful diagnostically in patients in whom there was some doubt about gluten sensitivity. Sensitivity to wheat gluten appears to be a feature of all cases of idiopathic steatorrhoea, but the reasons for variations in the quality and degree of sensitivity are unknown.

The role of vitamin D. Five patients (Cases 2, 3, 4, 7, and 8) showed evidence of resistance to the action of vitamin D while taking a normal diet, though they responded briskly to the same dose when receiving a gluten-free diet. In Cases 7 and 8 the addition of 2·5 mg. of calciferol daily, by intramuscular injection, failed to improve calcium absorption. This fact, together with the rapidity with which this phenomenon was reversed by changing from a gluten-free diet to a normal diet or vice versa, as well as the lack of correlation with the severity of the steatorrhoea, makes the hypothesis that osteomalacia is due simply to failure to absorb vitamin D virtually untenable. Our observations support the view held by the workers in Utrecht, that in coeliac disease there is a complex abnormality of intermediary metabolism. It is presumed that vitamin D is involved in this disorder and is inactivated, to some extent, when gluten is included in the diet. It is more justifiable to describe the rickets of coeliac disease, better called gluten enteropathy, as a vitamin-D resistant rickets, than to use this term

for the hereditary renal tubular defect associated with rickets which is, in fact, so called. This view is recommended by the fact that the rickets of gluten enteropathy is the more resistant of the two diseases to vitamin D. Case 9 exemplifies this resistance to vitamin D. The patient had received 2·5 mg. of calciferol by mouth daily for four months, increased to 15 mg. for a further six months, while taking an ordinary diet. In spite of these enormous doses the serum calcium remained below 10 mg. per 100 ml. throughout this period, and there was recurrence of bone pain. A gluten-free diet in gluten enteropathy must be considered as sensitizing the patient to the action of vitamin D, and not merely as improving intestinal absorption in general and fat, calcium, and vitamin-D absorption in particular.

The incidence of osteomalacia. Some further light may be shed upon the factors controlling the calcium balance and the incidence of osteomalacia if two groups of cases are abstracted from the present series.

Group I consists of four patients (Cases 1, 4, 5, and 7), and is characterized by the presence of osteomalacia, evidenced by pseudo-fractures or active rickets. It is surprising that three of these patients were in strongly positive calcium balance. The fourth (Case 4) had a slightly positive calcium balance. It must be noticed that at the commencement of study these patients had received no special diet and no vitamin D. In spite of a positive calcium balance they are not in remission so far as steatorrhoea is concerned. For osteomalacia to have developed, these patients must have been in negative calcium balance at some previous stage. It is probable that patients with steatorrhoea alternate between periods of positive and negative calcium balance, in spite of a consistent state of intestinal malabsorption as shown by increased faecal fat and flattened glucose-tolerance curves. These four patients had low serum inorganic phosphorus levels during the control periods. In Case 1 an increase accompanied the gluten-free diet, and calciferol produced an increase in the remaining three patients. A low serum inorganic phosphorus level would be consistent with secondary hyperparathyroidism, and indeed one patient (Case 5) showed radiological evidence of this condition.

Group II consists of two patients (Cases 2 and 3). The calcium balance was strongly negative in one (Case 2), and in the other the balance was zero. In spite of this there was no evidence of osteomalacia, although its occurrence would be inevitable if this state of affairs continued. It is equally certain that, since one of the patients had grown into an adolescent of normal size (Case 3) the zero calcium balance could not have persisted for very long.

Consideration of these two groups (Group I with osteomalacia and a positive calcium balance, and Group II with a negative calcium balance in a fully grown adult and zero balance in a growing adolescent without evidence of bone disease) strongly suggests that patients with steatorrhoea must alternate between periods of negative and positive calcium absorption. This ability to retain calcium, despite continued intestinal malabsorption in other respects, probably explains the rarity of bone disease in steatorrhoea (Lindsay, Nordin, and Norman, 1956). The low levels of serum inorganic phosphorus in associa-

tion with a positive calcium balance suggest the view that parathormone plays some part in this phasic variation in calcium absorption.

Similarities between vitamin D and parathormone are well recognized An example is provided by the difficulty in distinguishing between hypervitaminosis D and hyperparathyroidism. Albright and Reifenstein (1948) pointed out the increased renal clearance of phosphorus produced by vitamin D in patients who had undergone parathyroidectomy—an action qualitatively resembling that of parathormone. A condition closely resembling osteitis fibrosa cystica can be induced in rats on a low-calcium diet by giving large doses of calciferol (Jones and Rapaport, 1931). Patients with primary hyperparathyroidism may have such efficient calcium absorption from the gut that, in spite of an increased urinary excretion of calcium, they remain in positive balance (Albright, Bauer,

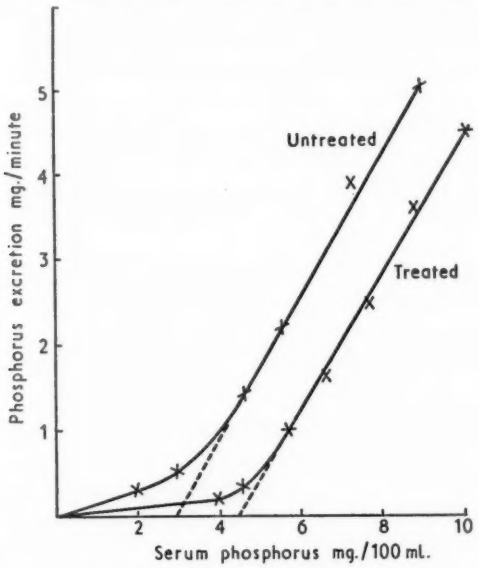

FIG. 10. Case 1. Result of phosphate infusions before and after treatment with calciferol.

Ropes, and Aub, 1953). It is suggested that parathormone may act as an endogenous substitute for an exogenous deficiency of vitamin D, and that the hormone has actions similar to those of the vitamin. It is presumed that the vitamin-D-like qualities of parathormone may be sufficiently effective to prevent the occurrence of osteomalacia in many patients with chronic steatorrhoea. The precise mechanism is unknown, and the theory one of conjecture; but possibly steatorrhoea leads to osteomalacia, with impaired calcium absorption a dominant feature. This impairment stimulates parathyroid secretion (Albright and Reifenstein, 1948), which in turn produces a diminution of serum inorganic phosphorus by a direct renal effect, and also promotes calcium absorption from the gut. A dynamic equilibrium is created, so that the amount of calcium absorbed from

the gut and the degree of hyperparathyroidism become stabilized. This stability is destroyed when normal mechanisms for calcium absorption come into action (gluten-free diet or effective doses of vitamin D). The sudden increase in serum inorganic phosporus is the immediate manifestation of this inhibition of parathyroid activity.

Fig. 10 shows the results of phosphate infusions given to one patient (Case 1) according to the method of Anderson (1955) both before and after treatment with calciferol. It was demonstrated that the rise in the level of serum inorganic phosphorus was due to greatly increased maximal renal tubular reabsorption of phosphorus.

Treatment. The presence of osteomalacia or rickets is an indication for a gluten-free diet, calciferol (0·25 to 0·5 mg. daily), and other vitamin supplements. Anaemia usually responds to a gluten-free diet, but folic acid and iron may hasten the initial response. Calciferol may be reduced considerably, and probably discontinued, after the bone disease is healed. Gluten-free diet needs to be continued indefinitely. Milder cases of steatorrhoea may be controlled without the difficulties of a gluten-free diet. Violent relapse follows discontinuation of a gluten-free diet, and this form of treatment should be recommended with circumspection if it is doubtful whether the patient will adhere to such a strict régime.

We are indebted to Dr. P. G. Walker, Biochemist to the Institute of Orthopaedics, for help and criticism, and to Dr. Harold Jory, who assisted with the clinical management of the patients. Our task has been made easier by assistance from Mrs. Glen Haig, the Hospital Records Officer, Mr. R. J. Whitley, in charge of the Department of Medical Photography, and Mr. C. Davenport, the librarian. Prolonged intensive metabolic studies of this kind depend for their success upon the efficiency and co-operation of all members of the metabolic unit. We are especially indebted to Sister D. T. Frazer, to our dieticians, Miss Carey, Miss Nancy Kirk, and Miss J. McLelland, and to the laboratory staff, Mr. John W. Woollen and Miss J. Collins.

Summary

Metabolic studies in nine consecutive cases of idiopathic steatorrhoea are presented. In all cases faecal fat and nitrogen were estimated, and in seven cases balance studies were made for calcium, phosphorus, and nitrogen. No consistent relationship could be demonstrated between the degree of steatorrhoea and calcium absorption. All the patients who had good calcium absorption at the time of study had active osteomalacia. It is suggested that such patients pass through phases of positive and negative calcium balance, and that this phasic variation is not related to the degree of steatorrhoea, but may be related to the degree of parathyroid activity. A marked increase in serum inorganic phosphorus followed treatment in six cases. It is suggested that this increase is a manifestation of parathyroid inhibition.

Many patients appeared to be highly resistant to the action of vitamin D, whether given orally or parenterally. This resistance was overcome by administering a gluten-free diet, but the patients became resistant again as soon as a normal diet was resumed.

The hypothesis that malabsorption of calcium in gluten enteropathy is due mainly or entirely to a primary absorption defect cannot be supported on the data presented. It is considered that, though there may well be such a defect, there is also a defect of intermediary metabolism involving vitamin D.

It was also noted that, although the response to a gluten-free diet was favourable in every case, reversion to a normal diet resulted in a relapse to a degree of steatorrhoea more severe than the original untreated condition. The advice to patients to take a gluten-free diet must therefore be tempered by the possibility that they may be worse if they are unable to maintain it rigidly.

ADDENDUM

Since submitting this paper we have learned that one patient (Case 2) was admitted to another hospital with persistent pyrexia. Physical examination and comprehensive investigations gave normal results, apart from anaemia (haemoglobin 10·8 g. per 100 ml.). The average daily faecal fat excretion was 2 g. with a continuing gluten-free diet. Laparotomy revealed a few abnormally enlarged mesenteric lymph-nodes, which histologically were characteristic of a reticulum-cell sarcoma. Liver biopsy performed at the same time showed normal histological appearances. The patient died suddenly in April 1958, but no necropsy was performed.

REFERENCES

Albright, F., Bauer, W., Ropes, M., and Aub, J. C. (1953) *Proc. roy. Soc. Med.* **46**, 1077.

—— and Reifenstein, E. C. (1948) *The Parathyroid Glands and Metabolic Bone Disease*, London.

Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., and Smellie, J. M. (1952) *Lancet*, **1**, 836.

—— —— —— Hawkins, C. F., Ross, A. C., and Sammons, H. G. (1954) *Gastroenterologia (Basel)*, **81**, 98.

Anderson, J. (1955) *J. Physiol. (Lond.)* **130**, 268.

Badenoch, J., and Fourman, P. (1954) *Quart. J. Med.* N.S. **23**, 165.

Barach, A. L., and Murray, H. A. (1920) *J. Amer. med. Ass.* **74**, 786.

Bassett, S. H., Keutmann, E. H., Hyde, H. van Z., Van Alstine, H. E., and Russ, E. (1939) *J. clin. Invest.* **18**, 101.

—— —— —— and Van Alstine, H. E. (1939) Ibid. **18**, 121.

Bauer, W., and Marble, A. (1932) Ibid. **11**, 21.

Briggs, A. P. (1922) *J. biol. Chem.* **53**, 13.

Clark, E. P., and Collip, J. B. (1925) Ibid. **63**, 461.

Dicke, W. K. (1950) *Coeliakie*, M.D. Thesis, Univ. of Utrecht.

—— Weijers, H. A., and van de Kamer, J. H. (1953) *Acta paediat. (Uppsala)* **42**, 34.

Findlay, L., and Sharpe, J. S. (1919) *Quart. J. Med.* **13**, 433.

Fourman, L. P. R., and Spray, G. H. (1948) *Brit. med. J.* **1**, 142.

Frazer, A. C. (1955) Ibid. **2**, 805.

French, J. M., Hawkins, C. F., and Smith, N. (1957) *Quart. J. Med.* N.S. **26**, 481.

Gerrard, J. W., Ross, C. A. C., Astley, R., French, J. M., and Smellie, J. M. (1955) *Quart. J. Med.* N.S. **24**, 23.
—— —— and Smellie, J. M. (1955) *Lancet*, **1**, 587.
Jones, J. H., and Rapaport, M. (1931) *J. biol. Chem.* **93**, 153.
Kamer, J. H. van de, and Weijers, H. A. (1955) *Acta paediat.* (*Uppsala*) **44**, 465.
—— —— and Dicke, W. K. (1953) Ibid. **42**, 223.
King, E. J. (1947) *Microanalysis in Medical Biochemistry*, London.
Koch, F. C., and McMeekin, T. L. (1924) *J. Amer. chem. Soc.* **46**, 2066.
Linder, G. C., and Harris, C. F. (1929) *Quart. J. Med.* **23**, 195.
Lindsay, M. K. M., Nordin, B. E. C., and Norman, A. P. (1956) *Brit. med. J.* **1**, 14.
McIver, C. (1952) *Lancet*, **2**, 1112.
Reifenstein, E. C., Albright, F., and Wells, S. L. (1945) *J. clin. Endocr.* **5**, 367.
Ruffin, J. M., Carter, D. D., Johnston, D. H., and Baylis, G. J. (1954) *New Engl. J. Med.* **250**, 281.
Sheldon, W., and Lawson, D. (1952) *Lancet*, **2**, 902.
Weijers, H. A., and van de Kamer, J. H. (1950) Centr. Inst. v. Voedingsonderzoek, T.N.O. Utrecht, Publn. No. 113.
Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E. (1947) *Gastroenterology*, **9**, 272.

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WHIPPLE'S DISEASE[1]

The Clinical Aspects

By P. FARNAN

(From the Department of Pathology, St. George's Hospital Medical School, London)

With Plates 16 to 18

Historical Outline

It is just over 50 years since the original case report from Johns Hopkins Hospital by Whipple (1907) on a young physician, who had been under observation in hospital for about one month, and had undergone laparotomy because of the presence of an abdominal mass. He died some weeks later 'rather suddenly', and at autopsy was found to have enlarged mesenteric and retroperitoneal lymph-nodes, pleuritis, pericarditis, and aortic endocarditis—a combination which, with the finding of peculiar 'polyblasts' in the jejunal mucosa and mesenteric lymph-nodes, was referred to as 'a hitherto undescribed disease'. The author, who was destined to pursue a most distinguished career in pathology, was awarded the Nobel Prize with Drs. Minot and Murphy in 1934. His original report remains the most complete description of the disease, and has dominated all subsequent papers on this condition.

Blumgart (1923) next described three cases of emaciation, anaemia, and malabsorption of fat, which he thought similar to the case described by Whipple, but at least two of these are not acceptable. The second generally acceptable case from America was reported, also from Johns Hopkins Hospital, by Jarcho (1936), nearly 30 years after the original paper. In the 13 years following this communication up to 1949 there were 14 papers on the subject, mostly single case reports, but those of Boeck (1938), Pearse (1942), and Pemberton, Comfort, Fair, and Zaslow (1947) illustrate the clinical and pathological uncertainties present during this period, and are not accepted as true examples. In America 13 cases had been reported up to the end of 1949, all in male subjects, and all having been diagnosed at autopsy. An attempt had been made by Rosen and Rosen (1947) to 'rectify the confusion' as to which cases should be included in the designation; but it was not until 1950 that the condition had attracted sufficient attention to warrant two reviews. In the first, Hendrix, Black-Schaffer, Withers, and Handler (1950) reported a series of four cases, including one diagnosed for the first time by mesenteric-node biopsy, and attempted to

[1] Received May 16, 1958.

re-define the disease. A much more exhaustive study was published later by Plummer, Russi, Harris, and Caravati (1950), which had the disadvantage of including a number of cases from the literature which had been discarded as unproved examples, though it brought into consideration several foreign case descriptions which had been neglected. In both instances the same general conclusions were drawn: that the condition was a definite entity, and that the accumulated data were sufficient to allow diagnosis from only the clinical history and physical signs.

At the same time Black-Schaffer (1949), who had undertaken a histochemical study of the macrophages found in the lamina propria of the jejunum and the mesenteric lymph-nodes in all cases of Whipple's disease, pointed out that these phagocytes contained material which stained deep scarlet when treated with Schiff's periodic-acid stain. He concluded from further investigations that the material was a glycoprotein—an observation which was doubly important: it provided a histological criterion for diagnosis, and it suggested a different view as to pathogenesis, which until then was thought to be an abnormality of fat metabolism.

Of the total of 46 cases from America, 28 have been reported since 1950, 10 being diagnosed before death, and five suspected on clinical grounds alone. A few small series are included: Russo (1952) reported two cases, Casselman, Macrae, and Simmons (1954) two cases, and Puite and Tesluk (1955) four cases. The last-named authors suggested that the only safe criterion for diagnosis was the demonstration of the characteristic macrophages; this principle had, however, already been accepted in America, and the cases of Jones, Benson, and Roque (1953), Lepore (1953), and Plummer, Weisiger, and Caravati (1953) had all been diagnosed during life by this means. There is a notable contrast between the present emphasis on ante-mortem diagnosis and therapy in the United States and the position on this side of the Atlantic. Sailer and McGann (1942) made reference to the European case reports of Fleischmann (1930) and Korsch (1938); but it was Clemmesen (1945) who co-ordinated the European and American literature on the subject, and mentioned for the first time the case reports of Fahr (1928), Hansen and von Staa (1936), Gaertner (1938), and Kloos (1939). None of these authors, except Clemmesen, used the term 'Whipple's disease', and this situation was commented upon three years later by Rutishauser, Demole, and Mach (1948), who remarked that in Europe 'every author . . . gives a new name to the anatomico-clinical picture which he is describing'.

Clemmesen's paper seems to have initiated in Europe a period of awareness of the disease comparable with the period 1936–49 in America: cases designated as Whipple's disease have since been reported from Germany by Frei (1947), from Switzerland by Rutishauser, Demole, and Mach (1948), from Holland by Mendes de Leon and Coenegracht (1952), and from Italy by Albertini (1952) and Inguscio (1952). It was not until 1949 that the first British case report appeared in which a definite diagnosis of the condition was made (Jones and Paulley, 1949). Previous reports by Glynn and Rosenheim (1938) and Vaux

(1943), although later accepted and proved as descriptions of the condition, had not mentioned Whipple's disease. There have been five British reports of single cases: those just mentioned, and those of Christie and Galton (1952) and Paulley (1952). All these communications are clinical in aspect, with the main emphasis on the intestinal manifestations and steatorrhoea. Leading articles and annotations in the *Lancet* (1953) and the *British Medical Journal* (1955, 1957), and a recent paper (Farnan, 1958), which is part of the present study, have drawn attention to the more widespread systemic features; but it is possible that the disease, both in its fully developed form and in its minor manifestations, is more common than has been suspected, and may often be classed in the general group of the idiopathic steatorrhoeas.

The Clinical Features

The present study is concerned with seven cases from this country, and with the clinical features of the 60 well-documented cases previously recorded. The main aetiological facts are well established: the disease occurs predominantly

TABLE I

The Prodromal Period

Average age at onset: 39 years. Average duration: four years.

	Duration					
	0–5 years		*5–10 years*			
Symptoms	*60 reported cases*	*Present series (7 cases)*	*60 reported cases*	*Present series (7 cases)*	*Total*	%
Asthenia . . .	14	4	Nil	Nil	18	27
Arthritis . . .	19	2	18	2	41	61
Diarrhoea . . .	40	1	4	1	46	69
Other abdominal symptoms:						
Anorexia . . .	16	3	1	Nil	20	30
Distension . . .	20	2	3	1	26	39
Constipation . .	12	3	Nil	Nil	15	22
Pain	25	3	9	1	38	57
Loss of weight:						
Mild	15	2	2	Nil	19	28
Moderate . . .	22	1	2	Nil	25	37
Severe . . .	10	2	Nil	Nil	12	18
Cough:						
Productive . . .	11	2	1	Nil	14	21
Non-productive . .	4	Nil	4	2	10	15

Totals and percentages are based upon those cases in which mention is specifically made of these symptoms.

in male subjects (55 out of the total of 67), and appears to be confined to the white races. It has been reported in siblings on one occasion (Puite and Tesluk, 1955). The average age on admission to hospital is 43 years, and a preceding period of prodromal symptoms, of varying duration, averages about four years.

I. *Prodromal period*

Protean symptoms of intermittent character have been known since Whipple

(1907) noted a 'peculiar multiple arthritis'. There are six cardinal features of this phase, all of which are intermittent in nature: arthritis, abdominal symptoms, diarrhoea, cough, loss of weight, and (less prominent) asthenia. They are important both because they assist clinical diagnosis of the fully developed disease, and because their character may help to explain its mechanism. The *arthritis* has been described in all degrees of severity, and can affect all joints, but has never resulted in residual deformity. *Gastrointestinal disturbances*, including both abdominal symptoms and disturbances of bowel function, are almost invariable. Vomiting is rare, but post-prandial attacks of upper abdominal pain, with distension or fullness, and often accompanied by upper abdominal tenderness, are common, and are apparently very suggestive of gall-bladder disease, cholecystectomy having been performed in a number of cases—those of Vaux (1943), Radding and Fiese (1954), Puite and Tesluk (Case 4) (1955), and Case 6 of the present series. Constipation and diarrhoea, sometimes alternating, are also very common, the severe onset of diarrhoea often necessitating admission to hospital; Amsterdam and Grayzel (1945) suggested that Whipple's disease should be included in the aetiological diagnosis of chronic diarrhoea. The occurrence of *cough*, productive or non-productive, is recorded in about one-third of the case reports. *Loss of weight* and *asthenia*, less frequently of intermittent character, show marked variation in degree and rate of onset, and merge with the fully developed picture usually seen in hospital.

II. *Period of decline*

The clinical picture of Whipple's disease is dominated by the observations made during the period in hospital, which, until the advent of steroid hormone therapy, was characterized by steady decline and a fatal outcome. The duration is much less varied, being between six and 15 months. The cause of admission is most frequently the gross exacerbation of any of the prodromal symptoms, or the onset of emaciation or asthenia. Many similar descriptions have been given of patients on admission: the subject is often an emaciated middle-aged man, with strong evidence of recent loss of weight and severe asthenia. The term 'chronic ill health' is used repeatedly in this connexion, for example by Fitzgerald and Kinney (1945), Newman and Pope (1948), Plummer, Russi, Harris, and Caravati (1950), and Lepore (1953). In contrast with this impression, two features have caused comment in a minority of cases: the mental state of the patient, and the appetite. The former aspect was of particular interest to Jones and Paulley (1949), who recognized an 'intestinal personality'; but more frequently the description is that of marked mental alertness. Odessky and Burdison (1950) noticed that in spite of the fact that their patient 'was chronically ill, he was well orientated and in good contact', and Lepore (1953) similarly recorded his patient as being 'alert, but chronically ill'. The same comment was made in the case reports of Apperley and Copley (1943) and Story and Sagild (1953); Jeckeln (1939) recorded the same general impression, noting that his patient had 'very shiny, alert, lively eyes which lay deep in their sockets'. A similar paradox has been noted by several observers with regard

to the appetite. Anorexia is common, and is frequently recorded as severe: it is almost invariably present at some stage of the illness; but a 'good' or 'very good' appetite has been recorded on a number of occasions. In this respect the most striking case is that of Hill (1937), who referred to the 'outstanding symptoms of ravenous appetite, somnolence and emaciation'; but Whipple (1907) had noted that 'in spite of continuous weight loss and severe diarrhoea the patient's appetite had always been good', and the striking difference between the state of the appetite and marked bodily ill health was commented upon by Glynn and Rosenheim (1938), Jarcho (1936), Odessky and Burdison (1950), Christie and Galton (1952), and Puite and Tesluk (Case 1) (1955). This feature is not common but, when present, apparently provides a striking clinical incongruity.

The Addisonian picture. The combination so often found of chronic ill health with asthenia, diarrhoea, hypotension, and skin pigmentation has repeatedly resulted in an initial clinical impression of Addison's disease. Skin pigmentation was present in about two-thirds of the reported cases: it has shown marked variation in distribution and intensity but, with the exception of one patient (Upton, 1952), it has not affected the buccal mucous membrane. It must be emphasized, however, that the results of all electrolyte investigations are normal, as is the excretion of 17-ketosteroids. The result of the Kepler test has also been recorded as normal in the great majority of cases in which it has been done, although an equivocal result was obtained by Upton (1952) and in Case 7 of the present series; but the clinical diagnosis of Addison's disease suggested itself to Glynn and Rosenheim (1938), Kampmeier and Peterson (Case 1) (1949), and Jones and Paulley (1949), as well as to Upton (1952). In two other reports (Sailer and McGann, 1942; Schutz, Benner, and Christian, 1949) the clinical impression of Addison's disease was such that the patient was treated accordingly, in spite of the lack of laboratory confirmation—a sequence of events which was repeated in Case 7 of the present series.

The physical findings. 1. *General examination.* Purpura was present in somewhat less than half of the patients. Like skin pigmentation, it shows much variation in distribution and severity. Oedema of the ankles was present in the same proportion of cases, but was usually slight. Peripheral lymphadenopathy, either generalized or localized to a single group of glands, was also present in about half the recorded cases (Table II). This feature has assumed importance since the observations of Upton (1952) and Puite and Tesluk (1955), confirmed in Case 5 of the present series, that the material characteristic of the disease could be demonstrated in the peripheral nodes.

2. *Systematic examination.* As a rule the alimentary system is the most deeply involved—a fact which has tended to obscure important supplementary observations in the respiratory and cardiovascular systems. Glossitis is rare, though recorded in case reports by Escudero, Mosto, and Landabure (1945) and Oliver-Pascual, Galan, Oliver-Pascual, and Castillo (1947), and observed in Case 6 of the present series. Its usual absence contrasts with the finding in idiopathic steatorrhoea, in which Snell (1939) found it to be almost invariably

present. On abdominal examination most reports record the presence of distension or meteorism, of indefinite tenderness, usually in the upper abdomen, or of an ill-defined abdominal tumour of variable size and position (Table II). Frequent attacks of abdominal distension, with marked discomfort, are mentioned by many authors, notably Apperley and Copley (1943), Odessky and Burdison (1950), and Casselman, Macrae, and Simmons (1954). This feature was particularly marked in Case 3 of the present series, in which attacks were said to have occurred over a period of 15 years. Tenderness is not usually

TABLE II

The Period in Hospital

Average age on admission: 43 years. Average duration: 10 months.

Clinical features	*60 reported cases*	*Present series (7 cases)*	*Total*	%
Asthenia	24	4	28	42
Emaciation	36	5	41	61
Hypotension	36	6	42	63
Pigmentation	36	5	41	61
Abdominal signs:				
Distension	23	6	29	43
Mass	14	1	15	22
Pain or tenderness	22	3	25	37
Ankle oedema	23	3	26	38
Lymphadenopathy:				
Localized	16	2	18	27
Generalized	7	3	10	15
Purpura	24	1	25	37
Fever	23	2	15	22
Heart murmurs	10	1	11	16
Scaly erythematous skin eruption	8	1	9	14
'Sudden' death	12	1	13	19

severe, but its site in the upper abdomen is frequently suggestive of gall-bladder disease. The presence of an ill-defined 'resistance' or 'mass' in the upper abdomen, usually in the left upper quadrant, has been noted by many authors, notably Whipple (1907), Fleischmann (1930), Korsch (1938), Reinhart and Wilson (1939), Raveno (1950), Casselman, Macrae, and Simmons (Case 1) (1954), Fisher and Whitman (1954), and Puite and Tesluk (Case 3) (1955). Ascites, hepatomegaly, or splenomegaly are not characteristic of the disease. Rarely the results of abdominal examination are negative, as in Russo's Case 2 (1952), and in Cases 2 and 5 of the present series.

Although endocardial vegetations are found *post mortem* in one-third of the patients (Table IV), and pleural fluid and adhesions in the majority, gross clinical evidence of disease in the cardiovascular or respiratory systems is uncommon. Nevertheless, heart murmurs have been commented upon in 10 case reports, notably those of Hendrix, Black-Schaffer, Withers, and Handler (Case 2) (1950), Casselman, Macrae, and Simmons (Case 1) (1954), and Fisher and Whitman (1954), while a severe degree of aortic incompetence was present in Case 1 of the present series. Similarly, physical signs related to the other thoracic organs are only infrequently recorded, in spite of the chronic cough

so often found. In Case 5 of the present series, however, respiratory manifestations dominated the clinical picture throughout; clinical or radiological evidence of pleural fluid or thickening may thus assist diagnosis in the context of other manifestations.

The remainder of the clinical observations are capricious and non-specific: fever is sometimes present, and tetany has been recorded twice, by Newman and Pope (1948) and Odessky and Burdison (1950). There is, however, one remarkable feature noted by several authors: the occurrence of 'sudden' death. An abrupt end was recorded by Whipple (1907), Apperley and Copley (1943), Fitzgerald and Kinney (1945), Christie and Galton (1952), and Luton (1952), among others. The last-named author thought the cause to be hypokalaemia; but electrolyte disturbances are rare and, since hypotension is common, a circulatory cause appears more probable. A number of authors, notably Upton (1952), have recorded that death 'occurred in a shock-like state'.

III. *Investigations*

The recorded results, as well as those found in the present series, are summarized in Table III. The findings can be broadly divided into two groups:

TABLE III

Laboratory Findings on 67 Cases of Whipple's Disease

Investigation	*Number of cases*	%
Chemical and metabolic disturbances:		
Increased faecal fat	30	45
Occult blood in stool	18	27
Flat glucose-tolerance curve	17	25
Low serum-calcium level (8–9·5 mg./100 ml.)	38	57
Plasma proteins:		
Low total	18	27
Reversed albumin/globulin ratio	9	13
Low serum-cholesterol level	2	
Increased serum glycoprotein	3	
Gastric achlorhydria	27	40
Electrolyte studies (Na, K, Cl)	Normal where examined	
Ketosteroid excretion	Normal where examined	
Blood changes:		
Anaemia:		
Normochromic	23	34
Hypochromic	23	34
Macrocytic	1	
White-cell count:		
Increased	18	27
Normal	24	36
Erythrocyte sedimentation rate increased	10	15
Vitamins:		
Vitamin-A deficiency	4	6
Vitamin B, C, D, and K	Normal where examined	

those common to most causes of steatorrhoea, which form part of the 'malabsorption syndrome', and those which are peculiar to the disease. The latter group includes the common finding of occult blood in the stools, the frequency

of gastric achlorhydria, which Snell (1939) found to be present in only seven of 32 cases of idiopathic steatorrhoea, and a normochromic or hypochromic anaemia, which is invariably present in Whipple's disease, but inconstant in idiopathic steatorrhoea. Radiological investigation has shown gastric or duodenal displacement or deformity in a small number of recorded cases, and in Cases 4 and 7 of the present series. Osteoporosis has not been recorded, but was present in six of Snell's (1939) series of cases of idiopathic steatorrhoea.

Case Reports

Case 1 (Isleworth). *Duration of prodromal period: five years. Duration of final period: two to three months.*

A man aged 37, who was in excellent health when discharged from the Army in 1945, began shortly afterwards to complain of epigastric pain, described as severe and gnawing in character, coming on immediately after food, and relieved by vomiting. The pain was diagnosed elsewhere as due to a duodenal ulcer, and for several years he continued to have periodic exacerbations of pain of moderate severity which, however, became very severe in the month before his first admission to hospital in July 1950. For several years before his admission there was a progressive gradual loss of weight, amounting to three stone. He admitted to suffering from a slight dry cough for years, was easily tired, and became breathless on slight exertion. His appetite had been poor for many months before admission, and he had suffered severely from constipation.

On examination the patient was thin, and showed obvious loss of weight. There was a generalized pigmentation of the skin (the patient volunteered that he had 'always been brown'), but no pigmentation of the buccal mucous membrane. A single large lymph-node was present in the left axilla, and 'shotty glands' in both groins. There was tenderness and guarding in the upper abdomen. The blood-pressure was 135/60, and a severe degree of aortic regurgitation was recorded, without any clinical evidence of cardiac enlargement. Barium-meal and X-ray examination confirmed the presence of a small duodenal ulcer. The blood picture showed a severe anaemia (haemoglobin 6·8 g. per 100 ml.), and the stool was strongly positive for occult blood. A fractional test meal showed only a small amount of free HCl (a factor which was remarked upon as unusual in the presence of an active duodenal ulcer), and the plasma proteins were 4·93 g. per 100 ml., with an albumin/globulin ratio of 0·68:1.

The patient did not respond particularly well to a medical régime, and after a few weeks, having had blood transfusion and general treatment, he was transferred for surgery. Serum Na, K, and Cl levels were determined before operation, and were all normal. Laparotomy was performed six weeks after his admission to hospital, and in addition to the chronic duodenal ulcer (treated by gastrectomy) there was gross enlargement of the lymph-nodes at the root of the mesentery, thought to be due to tuberculosis or lymphosarcoma; no biopsy of the nodes was done. A moderate amount of free fluid was also present in the abdomen. The jejunal mucosa, seen during gastrectomy, showed a 'curious silvery-white mottling', and a piece was taken for microscopy. It contained many fat-vacuoles and macrophages, and the association with enlarged mesenteric glands suggested the possibility of Whipple's disease. Accordingly the faecal fat was estimated, and found to amount to 25·2 per cent. of dried faeces—a very great increase above normal. The patient's condition after operation was satisfactory, and he was given a further blood transfusion:

a complete remission of his severe epigastric pain, and general improvement, allowed his discharge for out-patient observation two weeks after laparotomy.

He was readmitted to hospital, two months after discharge, because of attacks of vomiting during the previous five days. On examination there was a marked increase in pigmentation. He was also noted to have developed a more generalized discrete lymphadenopathy, the glands being small, firm, and mobile. During this period of observation, until his death six weeks later, his main complaint was of abdominal discomfort, with some nausea and vomiting. The stools were normally formed, although the fat content was still greatly increased. Anaemia was persistent, the haemoglobin falling to a level of 4·6 g. per 100 ml., and the stool was strongly positive for occult blood. The serum proteins had decreased to 4·1 g. per 100 ml., and the reversed albumin/globulin ratio noted previously was now more pronounced, being 0·5:1. Serum electrolyte levels (including Ca) were always normal. He deteriorated steadily, losing weight and strength, and died in a state of extreme cachexia.

Post mortem, in addition to the marked wasting and pigmentation present, many very small petechial haemorrhages were present on the forearms. The pleural cavities were not obliterated, and showed no adhesions or effusions. An embolus was present in one of the minor branches of the pulmonary artery, with infarction of the related portion of the lung. The pericardial cavity showed several areas of dense adhesions, but the cavity was not completely obliterated. In the heart there were large verrucous vegetations on the aortic and pulmonary valves, with partial destruction of the valve cusps. The coronary system and myocardium were both normal in appearance. In the abdominal cavity the mesenteric lymph-nodes were enlarged to 2 cm. in diameter, and when cut were greasy in consistency and showed many small cysts. Methylene blue injected into these nodes at the base of the mesentery was seen to pass along the mesenteric lacteals, and appeared in the thoracic duct. Enlarged lymph-nodes were also present in the neck, in both axillae, and at the bifurcation of the trachea. The spleen and liver both showed small patches of 'sugar icing' on the surface.

Histologically the lymph-nodes showed many large cystic spaces, containing sudanophil material and surrounded by a marked foreign-body giant-cell reaction. In the interstices of the lymph-nodes there were many macrophages which stained brilliantly with the periodic-acid Schiff reagent. The jejunal mucosa showed remarkable club-shaped villi, which were also distended by large numbers of macrophages surrounding large cystic, sudanophil-staining spaces, very similar to those seen in the lymph-node (Plate 17, Fig. 4). Examination of the other organs failed to reveal the presence of the characteristic macrophages. Sections of the thoracic duct appeared normal. No sections were made of the aortic valve vegetation.

Comment. In contrast to the notable lack of abdominal physical signs, the destruction of the aortic valve and the presence of vegetations on both the aortic and pulmonary valves resulted in a severe cardiovascular lesion. The presence of vegetations in these sites has been noted by many authors (in about one-third of the case reports). A diagnosis of aortic incompetence on clinical grounds has not been recorded hitherto, although the second patient of Hendrix, Black-Schaffer, Withers, and Handler (1950) was recorded as having systolic and diastolic murmurs at the apex, and the first patient of Casselman, Macrae, and Simmons (1954) had a 'soft blowing aortic diastolic murmur with cervical propagation'. In the present case the patency of the thoracic duct was

demonstrated (a point of obvious importance in view of the association of steatorrhoea and mesenteric adenopathy). The findings were similar in Whipple's patient, and also in the case described by Christie and Galton (1952). These observations cast doubt on the theory, advanced by many students of the condition, that inflammatory obstruction of the mesenteric lacteals is the explanation of the steatorrhoea.

Case 2 (Swindon). *No prodromal period. Duration of final period: 14 months.*

A man aged 48 was admitted to hospital for investigation of lower abdominal pain, which he had had for five weeks, and fairly severe diarrhoea, present for two weeks. In his family and personal history there was nothing relevant. General examination revealed only the presence of enlarged bilateral inguinal lymph-nodes, and a barium enema and chest X-rays were negative. The patient refused sigmoidoscopy and, since his presenting symptoms had improved, he was discharged from hospital. He was readmitted to hospital three and a half months later complaining of the onset of severe diarrhoea and a gross loss of weight.

On examination the patient was much wasted (Plate 16, Figs. 1 and 2), and showed pigmentation of the skin 'to the extent of a good sun-tan', which was of the same intensity all over the body. There was generalized lymphadenopathy, a moderate degree of ankle oedema, and fairly marked koilonychia, but again abdominal examination was recorded as 'negative'. There was a microcytic, hypochromic anaemia (haemoglobin 5·2 g. per 100 ml.). The stools were pale, frothy, and liquid, and showed a fat-content of 42 per cent. A glucose-tolerance test showed a very flat curve; the serum calcium was 8·5 mg. per 100 ml., and serum phosphorus 5·4 mg. per 100 ml. A lymph-node biopsy was undertaken, and was reported as showing a 'lymphohistiocytic medullary reticulosis'.

He showed some improvement on supporting therapy, including blood transfusions, and barium and X-ray examination of the intestine showed a 'deficiency pattern'; it was presumed that he had idiopathic steatorrhoea. After three and a half months in hospital he was discharged for the second time, but remained in poor health, suffering from many severe exacerbations of diarrhoea with short periods of remission, and becoming markedly asthenic. Although he failed to gain weight, his appetite was unimpaired. His downward course continued steadily, and once again he was admitted to hospital, where he was noted to have considerable abdominal distension (Plate 16, Fig. 3), and death occurred within a few days. The total duration of his illness had been 14 months.

Post mortem the body was extremely emaciated, the subcutaneous fat being almost non-existent. A purpuric rash was present on all limbs; there was generalized pigmentation of the skin, and moderate ankle oedema. There was marked abdominal distension, and the small intestine was thickened and pale in its upper third: the lymphatics showed up prominently as thick white lines. The pericardial cavity was obliterated by dense adhesions, and the aortic and tricuspid valve-cusps showed flattened, fibrinous vegetations on the edges of closure, and on the chordae tendineae of the mitral cusp. Large effusions, unsuspected clinically, were present in both pleural cavities, and a moderate amount of free fluid was present in the abdomen. Enlarged lymph-nodes were present in both the hilar region and the posterior mediastinum, as well as in the mesentery; the histological appearances of the jejunum and mesenteric lymph-nodes were as described in Case 1; in addition, the characteristic macrophages were found in the enlarged nodes in the mediastinum.

Case 3 (Swindon). *Duration of prodromal period: 10 months. Duration of final period: three and a half months.*

A man aged 63 had lost about three stone in weight in six months: his personal history showed him to have suffered from rheumatic fever at the age of 38, and he had been constipated for many years. He had suffered from periodic episodes of abdominal distension, and had an attack of bronchitis six months before his admission.

On examination the patient showed evidence of loss of weight. The only other findings on physical examination were a mild degree of ankle oedema and some abdominal swelling. His blood-pressure was recorded as 115/70, and the main investigations carried out were of the plasma proteins, which showed a level of 4·6 g. per 100 ml., the albumin/globulin ratio being 0·92:1; and of the blood, which showed a normochromic anaemia (haemoglobin 7 g. per 100 ml.). X-rays of the chest showed early Paget's disease of the spine. He was discharged without a diagnosis being established, but was readmitted four months later complaining of increasing swelling of the ankles and abdomen and severe constipation. An enema showed a pale, constipated stool, which had a fat-content of 18·4 per cent., of which 56 per cent. was unsplit. Laboratory examination showed a severe hypochromia (haemoglobin 5·7 g. per 100 ml.). Barium examination of the gastrointestinal tract revealed a 'deficiency pattern', and the patient was thought to have idiopathic steatorrhoea or 'subclinical' sprue; he was discharged, under treatment with folic acid, to be kept under observation.

He remained in poor health, losing weight constantly and being severely constipated. Oedema of the ankles recurred, and his abdomen became very swollen. During this time he complained of attacks of anorexia, but between these intermittent attacks his appetite was little impaired. He was readmitted to hospital, six months after his second discharge, because of the onset of sharp stabbing, substernal pain, and complaining of 'food sticking in his chest'; in hospital he was described as 'extremely emaciated, but not cachectic'. The main investigations carried out included the plasma proteins, which were 3·4 g. per 100 ml. with an albumin/globulin ratio of 0·42:1; blood urea, 125 mg. per 100 ml.; alkaline phosphatase, 5 units; serum calcium, 11 mg. per 100 ml., and serum phosphorus, 3·8 mg. per 100 ml. A fractional test meal showed an almost complete achlorhydria. His blood-pressure was recorded as 90/50, and fell still further before his death. In spite of his chronic illness, death occurred 'rather suddenly', about three weeks after his final admission. The total duration of his illness was 13½ months.

Post mortem there was a marked absence of depot fat, and a moderate degree of oedema of the ankles. There were small bilateral pleural effusions, and the abdominal cavity contained four pints of clear, pale yellow fluid. The intestine was normal in appearance; there was thickening and opacity of the splenic and liver capsules. The mesenteric lymph-nodes were enlarged up to 15 mm. in diameter, and were discrete, hard, and mobile; the para-aortic group of lymph-nodes were slightly enlarged, and showed a similar appearance. The mesenteric lacteals were prominent. Histology confirmed the presence of large numbers of Schiff-positive macrophages in the jejunal mucosa and mesenteric lymph-nodes.

Comment. This case was noteworthy in that marked constipation was present for many years, although diarrhoea is the more usual bowel disturbance; furthermore, there was no skin pigmentation or 'Addisonian' picture, a finding which is in agreement with the observation of Jones and Paulley (1949) that 'in every case where pigmentation is marked, diarrhoea has been present'. The clinical

observation that the patient was 'extremely emaciated, but not cachectic' probably records the difference between bodily and mental health which has been noted by a number of observers.

Case 4 (Southampton). *Duration of prodromal period: eight to nine years. Duration of final period: 18 months.*

This patient, an Army officer aged 47, had served abroad for several years: nine years before his presenting symptoms began he had suffered severely from 'sciatica and rheumatism', and for a number of years had been troubled by a chronic cough, much worse in winter, with which he had produced a moderate amount of sputum. His main initial complaint was of mild abdominal discomfort, which had commenced four months previously, occurring only occasionally at first, but later becoming more constant and described as 'gripping' in character. He also felt latterly as if his abdomen was 'full of wind'. In the same period he had lost three-quarters of a stone in weight. He had completely lost interest in food, finding it a 'nuisance to eat', and had noticed that his stools were pale in appearance. They were, however, normally formed, and at no time during this prodromal period was the patient troubled with diarrhoea.

On examination the patient was a poorly nourished, unwell-looking middle-aged man, showing marked asthenia. Physical examination records the abdomen as being 'slightly full' in the lower half; on palpation there was no evidence of an abdominal tumour, but the patient complained of 'soreness' in the umbilical region. The blood-pressure was 140/70, and the remainder of the physical examination showed nothing abnormal. Blood examination showed the haemoglobin to be 8·1 g. per 100 ml., white blood-cells 9,700 per cu. mm., and the erythrocyte sedimentation rate 39 mm. in one hour (Westergren); the blood films showed a hypochromic anaemia. The glucose-tolerance test showed a flat curve, and the faecal fat was 25 per cent. A fractional test meal showed normal gastric acidity, and examination of the stool for occult blood was negative. Liver-function tests gave normal results, and the serum proteins were 6·5 mg. per 100 ml., with a normal albumin/globulin ratio. X-rays of the abdomen showed several dilated, gas-filled loops of the intestine, and a few enlarged, radio-opaque lymph-nodes were present in the central abdomen (Plate 17, Fig. 5). X-rays of the chest showed no evidence of active tuberculosis, and a barium meal and follow-through showed only minor abnormalities in the region of the duodenal loop, the significance of which was uncertain; but because of these appearances the possibility of a carcinoma of the head of the pancreas, or chronic pancreatitis, was considered. His response to supporting therapy in hospital was satisfactory, and he was discharged after about five weeks.

Very shortly afterwards he suffered grievously from the onset of a severe and intractable diarrhoea, and deteriorated rapidly, with loss of weight and strength. He was readmitted to hospital, where on clinical and laboratory investigation the sole additional feature noted was a moderate generalized pigmentation of the skin. He remained three months in hospital on this occasion, being treated with blood transfusion and general supporting therapy, and later, empirically, with cortisone, and once again showed some general improvement, with cessation of diarrhoea. He was again discharged, but remained in poor general health, suffering from intermittent diarrhoea. After four months his general condition deteriorated rapidly, and on readmission he was found to be severely oedematous. Investigation showed a severe hypochromic anaemia, and a normal white-cell count. The serum proteins were 4·1 g. per 100 ml., with an

albumin/globulin ratio of 0·64:1. The serum sodium was 304 mg. per 100 ml., potassium 12·2 mg. per 100 ml., and chlorides 640 mg. per 100 ml. The serum calcium was 9·0 mg. per 100 ml. Cortisone therapy, previously effective, was on this occasion of no avail, and the patient died two weeks after admission.

Post mortem the body was extremely emaciated, and there was marked generalized pigmentation; many petechiae were present on all the limbs and on the trunk. The pleurae and pericardial cavities were obliterated by adhesions; the mitral valve of the heart showed flattened vegetations on the opposing surfaces. The intestine was of normal appearance, but the mesenteric and para-aortic groups of lymph-nodes were enlarged, homogeneously white, and hard in consistency: there was no evidence of cysts on the cut surface, such as are usually found (Plate 18, Fig. 7). Histologically the architecture of the lymph-nodes was replaced by excessive numbers of characteristic macrophages; only a few very small cystic areas were present.

Comment. The suggestion of extra-alimentary malignancy, due to duodenal distortion on barium examination, has been recorded in a minority of cases. Radio-opaque mesenteric nodes were also recorded by Christie and Galton (1952), and in the present case are probably related to the very large amounts of material in the nodes staining with the periodic-acid Schiff reagent.

Case 5 (Dartford). *Duration of prodromal period: two and a quarter years. Duration of final period: six months.*

A man aged 54 had come under observation, two years before his final admission to hospital, with a three-month history of weakness, loss of weight, and dyspnoea on exertion. These symptoms had followed an attack of bronchitis; examination showed a small amount of fluid in the left pleural cavity and a severe hypochromic anaemia (haemoglobin 6 g. per 100 ml.). He improved after blood transfusion, but remained in indifferent health in the interval before his final admission. His main symptoms during this time were dyspnoea and persistent productive cough, with asthenia, loss of weight, and 'fullness' in the epigastrium after meals. He was admitted to hospital because of the acute exacerbation of his respiratory symptoms.

Examination showed scattered physical signs in the lungs, patchy pigmentation of the skin, and a discrete generalized lymphadenopathy. Blood examination showed a severe degree of hypochromic anaemia (haemoglobin 8 g. per 100 ml.). All electrolyte investigations gave normal results, and the sputum showed no evidence of tubercle bacilli. A lymph-node biopsy showed 'several follicular structures, composed of epithelial cells, suggestive of Boeck's sarcoid'. X-ray examination of the chest showed pleural thickening and adhesions, and later a hilar opacity. During this period of observation in hospital there was an almost complete absence of abdominal and bowel symptoms. The patient remained in hospital for two months, losing weight and strength before his death.

Post mortem, apart from severe wasting and skin pigmentation, the main findings were present in the thorax. There was enlargement of the hilar glands on the right side, with patchy atelectasis of the right lower lobe. The pericardial and pleural cavities were obliterated by adhesions. The myocardium and endocardium were normal. In the abdomen a moderate amount of free straw-coloured fluid was present, with enlargement of the lymph-nodes in the root of the mesentery and para-aortic regions. The adrenal glands were embedded in oedematous periadrenal tissue. On histological examination, in addition to the large numbers of 'Schiff-positive' macrophages in the mesenteric lymph-nodes

and small intestine, small numbers were observed beneath the epicardium and in the subpleural and periadrenal tissues. Further sections, taken in retrospect from the original axillary lymph-node biopsy specimen, showed a few aggregations of the macrophages in the depths of the follicles (Plate 18, Fig. 6).

Comment. The presenting features in this case are unusual, in that respiratory symptoms are as a rule most marked in the prodromal period, and during the period in hospital are overshadowed by the abdominal manifestations. The 'sarcoid-like' picture on peripheral lymph-node biopsy has also been recorded by Russo (Case 2) (1952), Fisher and Whitman (1954), Upton (1952), and Puite and Tesluk (1955); the last-named authors found aggregations of the macrophages by re-examining the material. The confirmatory observation in the present case was made possible through the courtesy of Dr. M. O. Skelton of Lewisham Hospital. This case is also similar to that reported by Upton (1952) in revealing a widespread extra-abdominal dissemination of foam-cells.

Case 6 (Liverpool). *Duration of prodromal period: 23 years. Duration of final period: five months.*

The past history of this patient showed that 23 years before her final presentation she had spent three weeks in hospital in the United States suffering from severe diarrhoea and gnawing epigastric pain, which was unrelated to food. For six months before her admission to hospital in this country she had noticed a deterioration in her appetite and some loss of weight.

On examination the patient was anaemic (haemoglobin 6·2 g. per 100 ml.), and the only positive physical sign was acute tenderness just below the xiphisternum; a diagnosis of cholecystitis was made, and a cholecystectomy performed. Several lymph-nodes were palpated in the root of the mesentery, but were apparently not taken for examination. The gall-bladder was normal on gross and microscopical examination, and the patient was discharged, three weeks after operation, free from symptoms. She subsequently remained in relatively good health, but from time to time suffered recurrence of her upper abdominal pain, and from periodic short attacks of anorexia, fever, and diarrhoea. These episodes, however, were usually of short duration, and did not require hospital investigation or treatment. She finally came to hospital with a history of intermittent attacks of diarrhoea for two months before admission.

On examination there was marked loss of weight and asthenia, and a raised and swinging temperature. There was marked glossitis, and some abdominal distension; the breath sounds were impaired over the lower lobe of the right lung. Chest X-rays showed consolidation with effusion, although the patient had no chest symptoms. Barium examination of the stomach and bowel gave normal results, and a fractional test meal showed gastric achlorhydria. There was a moderately severe normochromic anaemia, the haemoglobin level falling from 12 g. to 7·5 g. per 100 ml. There was a persistent leucopenia (white cells 3,100 to 2,000 per cu. mm.); the plasma proteins were 4·8 g. per 100 ml., with an albumin/globulin ratio of 1·7:1. Faecal-fat estimations showed that 26·4 per cent. by weight of dried faeces was fat, 65 per cent. of which was split; the stool contained occult blood. The patient showed little response to supporting therapy, and developed a scaling erythematous eruption of the hands and arms; later there were marked petechial haemorrhages on the arms and trunk. She became extremely pigmented, and while in hospital developed moderate oedema

of both ankles. She continued to lose strength, and her blood-pressure towards the end was 90/60. She died about five months after admission, and was thought to have had a sprue syndrome secondary to tuberculous enteritis.

Post mortem there was severe wasting, and generalized pigmentation of the skin. The mesenteric lacteals of the small intestine were dilated and prominent. A group of lymph-nodes was found in the root of the mesentery; they contained small cysts, and were greasy in consistency. In the thorax there was collapse and consolidation of the right lower lobe of the lung, with a small pleural effusion. The left pleural cavity was obliterated by adhesions: the heart showed no evidence of endocardial lesions. The histological findings were as described in Cases 1 and 2.

Comment. Cholecystectomy, as already mentioned, has sometimes been carried out because of the suggestive site and character of the upper abdominal pain. One such case—that described by Jones, Benson, and Roque (1953)—also occurred in a female subject; but those of Vaux (1943) and Radding and Fiese (1954) both occurred in men. The presence of glossitis is unusual.

Case 7 (Kingston). *Duration of prodromal period: four years. Duration of final period: five months.*

The patient, a man of 48 years, had complained of occasional aches in the limbs for one year before his first admission, and had noticed occasional slight swelling of the ankles and finger-joints. He had been treated four years previously for an 'adhesion capsulitis' of the right shoulder joint. For four months before coming under observation he had been 'feeling tired easily', and eventually he was forced to stop work.

Examination showed pallor of the mucous membranes, moderate generalized pigmentation of the skin, and a mild fever. There was slight enlargement of lymph-nodes in the left axilla, but the respiratory, cardiovascular, and alimentary systems showed no abnormality. The initial clinical impression was of Addison's disease, but apart from a severe hypochromic anaemia (haemoglobin 7·2 g. per 100 ml.), a neutrophile leucocytosis of 14,200 cells per cu. mm., and an equivocal Kepler test on one occasion, all laboratory investigations, including electrolyte estimations, gave normal results. The patient's strength improved with rest in bed and a low-salt diet, and he was discharged for out-patient observation. He continued to show some gain in weight and strength, but subsequently developed a diffuse abdominal distension and bilateral inguinal lymphadenopathy; an indefinite mass could be felt in the left upper quadrant of the abdomen, and a barium meal showed displacement of the stomach to the left, and possibly a deformity of the second part of the duodenum. There were, however, no symptoms referable to the alimentary system, and results of laboratory investigations remained within normal limits.

After being under observation for 10 months he was readmitted to hospital, having had severe diarrhoea for four weeks and a loss of weight of one stone over the same period. The patient was ill and dehydrated, but without fever, and there was a marked glossitis, but no other physical signs. A barium meal showed the same appearance as previously, with displacement of the stomach and duodenum to the left. The stools contained occult blood, and were bulky, containing 44 per cent. of fat by weight, 85 per cent. of which was split. The anaemia was severe, and hypochromic in type. In spite of supporting therapy, including iron, vitamins, and blood transfusion, the patient steadily deteriorated,

and died in a state of great emaciation. Cortisone administered in the later stages of the illness had no effect.

Post mortem there was marked abdominal, cervical, and thoracic adenopathy. The pericardial sac was obliterated by thick fibrous adhesions, and plaque-like vegetations, varying from 0·5 to 1·5 cm. in diameter, were present on the cusps of the mitral, tricuspid, and pulmonary valves. Smaller, similar plaques were present on the chordae tendineae and endocardium of both ventricles. The left hip- and knee-joints were macroscopically normal. Histologically the abdominal lymph-nodes and jejunum showed the characteristic appearance. The plaques on the heart valves were made of mixed vascular, cellular, and hyalinized collagen, which contained various-sized collections of Schiff-positive macrophages and siderophages. The plaques were demarcated from the underlying cusp by a surviving undestroyed lamina of elastic fibres.

Comment. The presentation of this disease in the form of an Addisonian syndrome unsupported by laboratory investigation is well illustrated by this case, and appears to be related to the steatorrhoea. The finding of an indefinite mass in the left upper abdomen has been recorded by a number of observers, and was similarly described by Raveno (1950). It is due to the presence of fairly gross adenopathy in the pancreatic and para-aortic regions, which may also cause displacement of the stomach and duodenum, visible on X-ray examination. The combination of an extragastric mass, duodenal distortion, and steatorrhoea, may sometimes suggest a slowly growing carcinoma of the pancreas. Upton (1952) appears to have been the only other author to record the presence of the characteristic macrophages in the vegetations of the heart valves.

Discussion

Until the advent of steroid therapy a fatal outcome of the disease appears to have been invariable; the sole exception recorded is the case reported by Pearse (1942), which, partly at least because of this result, has not been generally accepted as an example of Whipple's disease. The results of steroid therapy are capricious, but remission of some degree appears to be the rule, though eventually followed by relapse and death, as reported by Mendes de Leon and Coenegracht (1952), Plummer, Weisiger, and Caravati (1953), and Radding and Fiese (1954). In a number of recent reports, notably those of Jones, Benson, and Roque (1953), Lepore (1953), and Wang, Janowitz, and Adlersberg (1956), remissions have been longer, although exacerbations have occurred in the course of therapy.

There are no grounds for assuming a pituitary-adrenal mechanism to explain the main features of the condition. The pathogenesis has never been clear: innumerable theories have been advanced which, until 1950, suggested a fundamental abnormality of fat metabolism. The demonstration by Black-Schaffer (1949) of a mucopolysaccharide complex in the macrophages in the jejunum, which has been confirmed by subsequent observers (Casselman, Macrae, and Simmons, 1954; Farnan, 1958), caused a reorientation of aetiological concepts, and it now appears likely that the jejunal mucosa represents the source of the

process. An abnormality of mucus secretion in this region appears unlikely: differential staining shows the characteristic material to be sharply confined to the lamina propria and the underlying lacteals, while mucus secretion appears to have been proceeding normally (Farnan, 1958). Thus an alteration in the mucopolysaccharide ground-substance of this region may be the basic abnormality. The possibility of a genetic predisposition is suggested by the similarity in age at onset, the predominance of the male sex, and the occurrence of the disease in siblings reported by Puite and Tesluk (1955).

TABLE IV

The Main Gross and Microscopic Findings at Autopsy in 67 Cases of Whipple's Disease

Finding	*60 reported cases*	*Present series (7 cases)*	%
Mesenteric adenopathy (with Schiff-positive macrophages)	56	7	94
Similar macrophages in jejunal mucosa	54	7	91
Marked loss of subcutaneous fat	50	6	84
Skin pigmentation	36	5	61
Petechial haemorrhages in skin	24	3	40
Peripheral lymphadenopathy:			
Localized	16	2	27
Generalized	7	3	15
Adenopathy elsewhere, e.g. thorax, para-aortic regions	18	6	36
Involvement of serous cavities:			
Pericardial fluid	6	2	12
Pericardial adhesions	21	6	40
Subepicardial macrophages (Schiff-positive)	1		
Pleural fluid	10	3	19
Pleural adhesions	17	3	30
Subpleural macrophages (Schiff-positive)	1		
Peritoneal fluid	10	3	19
Peritoneal adhesions	7	1	12
Thickening and 'sugar-icing' of:			
Splenic capsule	13	3	24
Liver capsule	9	3	18
Endocardial vegetations:			
Aortic valve	8	2	15
Mitral valve	8	2	15
Tricuspid valve	7	2	13
Pulmonary valve	Nil	1	
Schiff-positive aggregations in vegetations	1	1	3
Histological foci of macrophages elsewhere	1	1	
Schiff-positive macrophages in peripheral lymph-nodes	3	1	6

Although the features due to malabsorption have dominated the clinical concept of the condition, a possible explanation of the systematic lesions, which are summarized in Table IV, is the finding of the characteristic material in widespread sites in a minority of cases. Thus Upton (1952) reported it to be demonstrable in the retroperitoneal tissues, liver, spleen, and heart-valve vegetations (in which it was also seen in Case 7 of the present series); the macrophages have been demonstrated in the peripheral lymph-nodes by Upton (1952) and Puite and Tesluk (1955), as well as in Case 5 of the present series, in which they were also demonstrated in the subpleural, subepicardial, and

periadrenal tissues. These findings, with the exacerbations of acute illness which characterize the prodromal period, may represent the intermittent formation of the material and its dissemination through the thoracic duct and by the blood-stream (Farnan, 1958).

The main features of the condition seen during the final period in hospital are accounted for by the steatorrhoea which is constantly present. An obstructive lesion affecting either the mesenteric lymph-nodes or the thoracic duct has been inferred by many authors; the duct, however, has been found patent whenever examined, for example, by Whipple (1907) and Sailer and McGann (1942), and in Case 1 of the present series. Nevertheless, formation of the Schiff-positive material in excess may eventually lead to lacteal obstruction at the mucosal site—an idea which gains support from the appearance of the large fat-containing spaces in the club-shaped villi, closely surrounded by large amounts of the material, which is an invariable finding *post mortem* (Plate 17, Fig. 4.) A similar mechanism may also be responsible for the finding of dilated fat-filled spaces in the mesenteric lymph-nodes.

My thanks are due to several clinicians and pathologists who have allowed me to examine their patients or material, or have directed attention to possible sources. In particular I am indebted to Professor T. Crawford for advice, and for undertaking most of the photography included in the paper, and to Drs. K. M. Robertson, Senior Physician, and R. A. Goodbody, Consultant Pathologist of the Royal South Hants Hospital, Southampton, for their interest and encouragement. The paper is part of a report awarded a Registrar's research prize (1957) by the South-West Metropolitan Regional Hospital Board.

Summary

1. A study has been made of a series of seven cases of Whipple's disease. With the cases previously reported, the present study indicates a clinical pattern which may be divided into a prodromal period, characterized by exacerbation of illness, and a final period of relatively rapid decline. The condition may be more common than is suspected, and should be included in the diagnosis of the steatorrhoeas and the causes of chronic diarrhoea.

2. The fully developed picture often suggests Addison's disease; the absence of electrolyte disturbances should allow Whipple's disease to be considered.

3. The main physical signs are usually found on abdominal examination. The triad of distension, upper abdominal mass, and radiological evidence of gastric or duodenal displacement, or any two of these features, may be of help in diagnosis. Supporting evidence may be available in the cardiovascular or respiratory system.

4. The results of laboratory investigations parallel those found in idiopathic steatorrhoea; but the invariable presence of a normochromic or hypochromic anaemia, the finding of occult blood in the stools, and the common association of gastric achlorhydria, may help to differentiate the conditions.

5. The diagnosis is confirmed only if the characteristic Schiff-positive macrophages are found. Mesenteric-node biopsy may often be necessary for this purpose, but they have been demonstrated in peripheral lymph-nodes, and lymphadenopathy with an indefinite 'sarcoid-like' picture should stimulate search of lymph-nodes taken by biopsy.

6. The basic lesion appears to be an alteration in the ground-substance of the mucosa of the jejunum. Its periodic formation and dissemination may account for the protean symptoms of the prodromal period, and for the extensive lesions found at autopsy; later, when produced in excess, it appears to cause obstruction of the lacteals at the mucosal site and the clinical features of a general malabsorption defect.

Author's present address: Department of Pathology, West Kent General Hospital, Maidstone, Kent.

REFERENCES

Albertini, B. (1952) *Arch. ital. Mal. Appar. dig.* **18,** 195.
Amsterdam, J. J., and Grayzel, D. M. (1945) *Amer. J. Med. Sci.* **210,** 605.
Apperley, F. L., and Copley, E. L. (1943) *Gastroenterology,* **1,** 461.
Black-Schaffer, B. (1949) *Proc. Soc. exp. Biol. (N.Y.)* **72,** 225.
Blumgart, H. L. (1923) *Arch. intern. Med.* **32,** 113.
Boeck, W. C. (1938) *Amer. J. dig. Dis.* **4,** 731 (in discussion).
British Medical Journal (1955) **1,** 191 (Annotation).
—— (1957) **1,** 998 (Leading article).
Casselman, W. G. B., Macrae, A, I., and Simmons, E. H. (1954) *J. Path. Bact.* **68,** 67.
Christie, A. C., and Galton, D. A. G. (1952) Ibid. **64,** 351.
Clemmesen, J. (1945) *Acta. med. scand.* **121,** 495.
Escudero, P., Mosto, D., and Landabure, P. B. (1945) *Dia méd.* **17,** 915.
Fahr, T. (1928) *Klin. Wschr.* **7,** 1787.
Farnan, P. (1958) *J. Clin. Path.* **11,** 382.
Fisher, E. R., and Whitman, J. (1954) *Cleveland Clin. Quart.* **21,** 213.
Fitzgerald, P. J., and Kinney, T. D. (1945) *Amer. J. Path.* **21,** 1069.
Fleischmann, R. (1930) *Arch. klin. Chir.* **158,** 692.
Frei, R. (1947) *Schweiz. Z. allg. Path.* **10,** 685.
Gaertner, K. (1938) *Frankfurt. Z. Path.* **52,** 529.
Glynn, L. E., and Rosenheim, M. L. (1938) *J. Path. Bact.* **47,** 285.
Hansen, K., and von Staa, H. (1936) *Die einheimische Sprue und ihre Folgekrankheiten sekundäre Avitaminosen*), p. 39. Leipzig.
Hendrix, J. P., Black-Schaffer, B., Withers, R. W., and Handler, P. (1950) *Arch. intern. Med.* **85,** 91.
Hill, J. M. (1937) *Amer. J. Path.* **13,** 267.
Inguscio, L. (1952) *Athena (Roma),* **18,** 315.
Janowitz, H. D., Drachman, S. R., Wang, C. I., and Adlersberg, D. (1952) *Proc. Amer. gastroenterol. Ass.* May 2nd.
Jarcho, S. (1936) *Bull. Johns Hopk. Hosp.* **59,** 275.
Jeckeln, F. (1939) *Virchows Arch. path. Anat.* **303,** 393.
Jones, C. M., Benson, J. A., and Roque, A. L. (1953) *New Engl. J. Med.* **248,** 665.
Jones, J. F. A., and Paulley, J. W. (1949) *Lancet,* **1,** 214.
Kampmeier, R. H., and Peterson, J. C. (1949) *Trans. Amer. clin. climat. Ass.* **61,** 248.
Kloos, K. (1939) *Virchows Arch. path. Anat.* **304,** 625.

Korsch, J. H. (1938) *Zbl. allg. Path. path. Anat.* **71**, 337.
Lancet (1953) **2**, 79 (Annotation).
Lepore, H. (1953) *Amer. J. Med.* **17**, 160.
Luton, E. F. (1952) *Gastroenterology*, **20**, 327.
Mendes de Leon, C., and Coenegracht, J. (1952) *Ned. T. Geneesk.* **96**, 560.
Newman, B., and Pope, R. H. (1948) *Gastroenterology*, **11**, 120.
Odessky, L., and Burdison, W. R. (1950) *Arch. Path.* (*Chicago*) **49**, 307.
Oliver-Pascual, E., Galan, J., Oliver-Pascual, A., and Castillo, E. (1947) *Rev. esp. Enferm. Apar. dig.* **6**, 213.
Paulley, J. W. (1952) *Gastroenterology*, **22**, 128.
Pearse, H. E. (1942) *Surgery*, **11**, 906.
Pemberton, J. de J., Comfort, M. W., Fair, E., and Zaslow, J. (1947) *Surg. Gynec. Obstet.* **85**, 85.
Plummer, K., Russi, S., Harris, W. H., Jnr., and Caravati, C. M. (1950) *Arch. intern. Med.* **86**, 280.
—— Weisiger, B. B., and Caravati, C. M. (1953) Ibid. **91**, 784.
Puite, R. H., and Tesluk, H. (1955) *Amer. J. Med.* **19**, 383.
Radding, J., and Fiese, M. J. (1954) *Ann. intern. Med.* **41**, 1066.
Raveno, W. S. (1950) *New. Engl. J. Med.* **243**, 216.
Reinhart, H. L., and Wilson, S. J. (1939) *Amer. J. Path.* **15**, 483.
Rosen, M. S., and Rosen, S. H. (1947) Ibid. **23**, 443.
Russo, F. R. (1952) *A.M.A. Arch. intern. Med.* **89**, 600.
Rutishauser, E., Demole, M., and Mach, R. S. (1948) *Rev. méd. Suisse rom.* **68**, 573.
Sailer, S., and McGann, R. J. (1942) *Amer. J. dig. Dis.* **9**, 55.
Schutz, P. J., Benner, W. H., and Christian, W. A. (1949) *Amer. J. Med.* **7**, 553.
Snell, A. M. (1939) *Ann. intern. Med.* **12**, 1632.
Story, R. D., and Sagild, U. (1953) *J. Amer. med. Ass.* **152**, 312.
Upton, A. C. (1952) *Amer. J. clin. Path.* **22**, 755.
Vaux, D. M. (1943) *J. Path. Bact.* **55**, 93.
Wang, C. I., Janowitz, H. D., and Adlersberg, D. (1956) *Gastroenterology*, **30**, 475.
Whipple, G. H. (1907) *Bull. Johns Hopk. Hosp.* **18**, 382.

FIG. 1

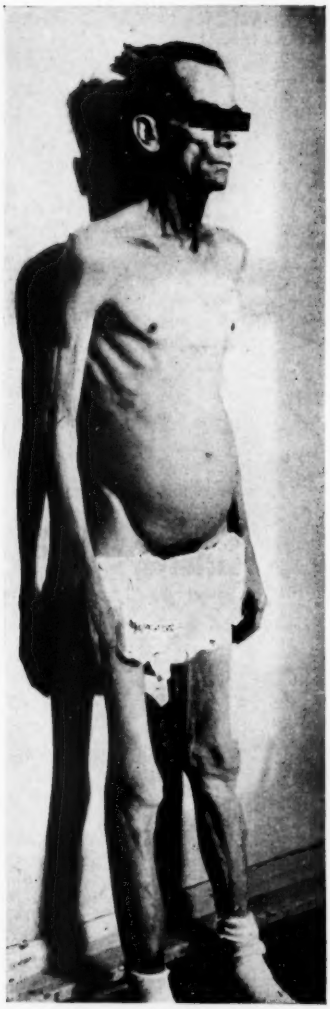


FIG. 2

FIGS. 1 and 2. Case 2. The photographs show marked loss of subcutaneous fat

FIG. 3. Case 2. Abdominal distension is a marked feature of the fully developed disease

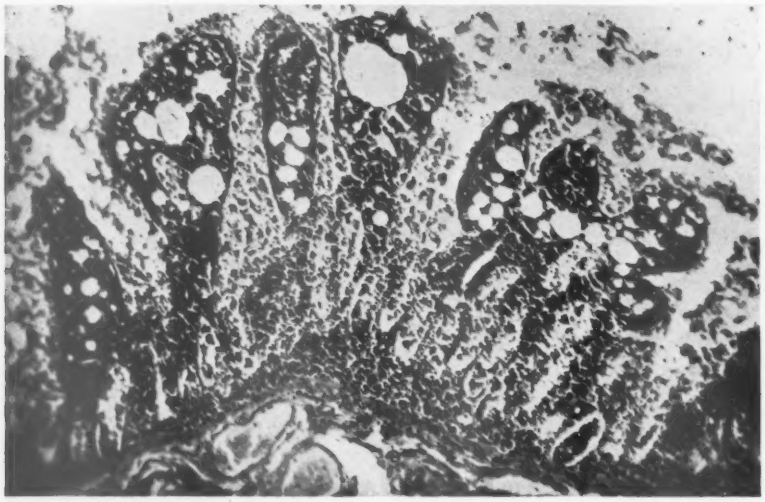


FIG. 4. The distended club-shaped folds of the jejunal mucosa show fat-filled spaces, around which are large numbers of macrophages containing granules staining with periodic-acid Schiff reagent (×67)

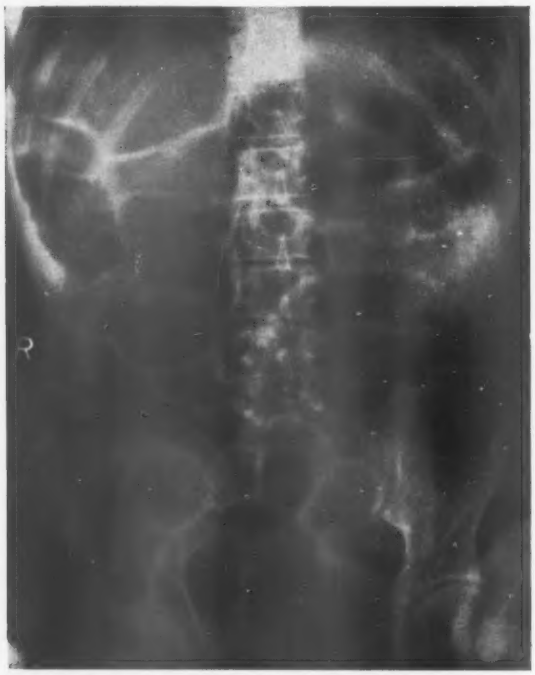


FIG. 5. Case 4. Radiograph of the abdomen showing a group of enlarged radio-opaque lymph-glands arranged along the superior mesenteric artery

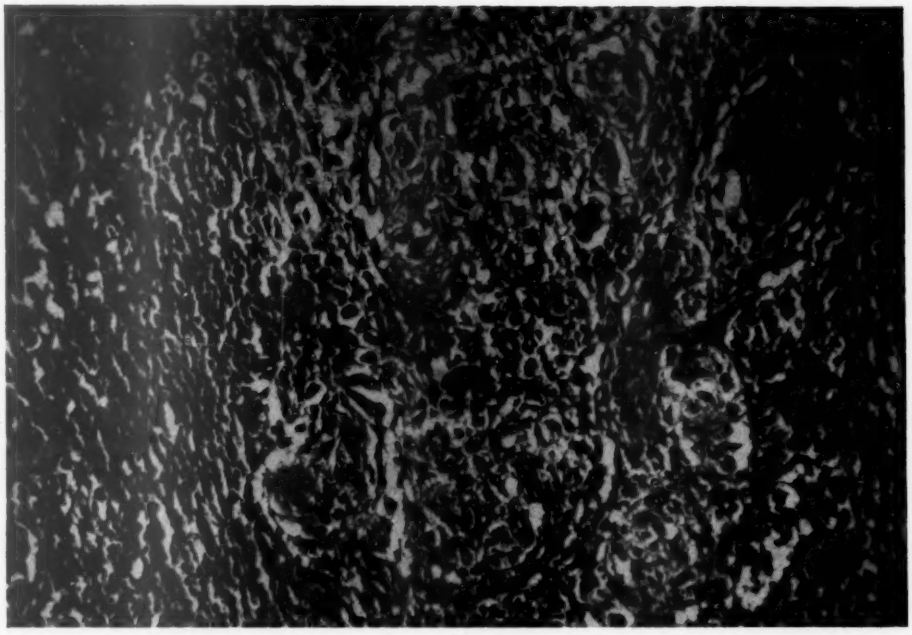


FIG. 6. Case 5. The 'sarcoid-like' follicles in the axillary lymph-node are composed of epithelioid cells and a few giant cells. Scattered periodic-acid-Schiff-staining macrophages, arranged singly or in small groups, are present in the depth of the follicle (×170)

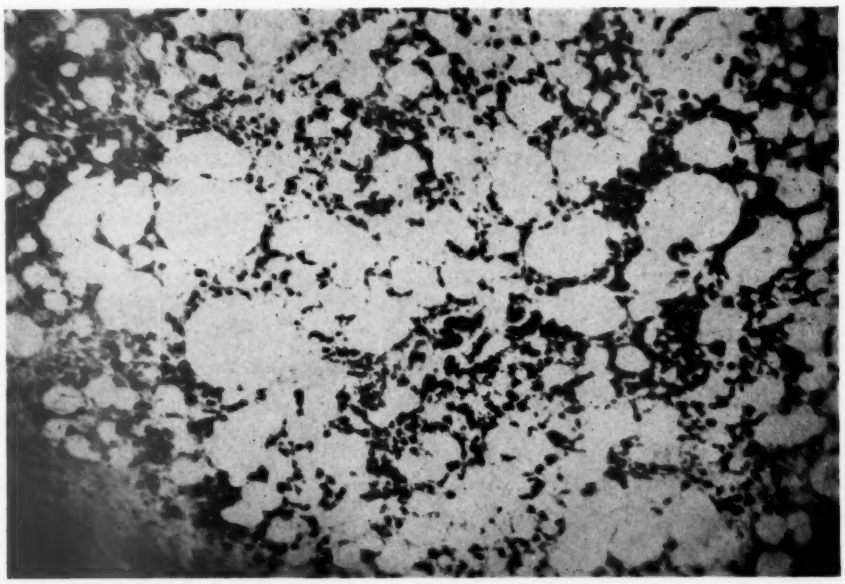


FIG. 7. Widely dilated fat-containing spaces in the mesenteric lymph-node are interspersed with moderate numbers of characteristic macrophages (×80)

616-008.823.979.733

ACUTE INTERMITTENT PORPHYRIA[1]

A Study of 50 Cases

By A. GOLDBERG

(From the University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow,[2] and the Department of Chemical Pathology, University College Hospital Medical School, London)

The porphyria group of diseases consists of acute intermittent porphyria, porphyria cutanea tarda, and congenital porphyria. Acute intermittent porphyria is the most important member of the group, and is clinically distinguishable from the other two by the dominance of gastrointestinal and neurological symptoms and the absence of skin photosensitivity. In the acute phase of this disease, and often in states of remission, patients excrete in the urine large amounts of porphobilinogen, a colourless chromogen which on the addition of Ehrlich's aldehyde reagent forms a red compound insoluble in chloroform. Porphobilinogen is never excreted in congenital porphyria, and rarely in porphyria cutanea tarda. Since Stokvis first described the condition in 1889, there have been few comprehensive clinical reviews (Günther, 1911, 1922; Waldenström, 1937), although there have been many reports of small numbers of cases. In the past decade important advances have been made in the biochemistry related to this disease. The most relevant to the clinical problem has been the isolation and identification of porphobilinogen, the characteristic excretion product. By paper chromatography it is now possible to detect the presence of small amounts of this substance. This method, applied to the urine of relatives of sufferers, has allowed the detection of latent cases which would otherwise have been unrecognized. Recent work on the pharmacology, neuropathology, and experimental pathology of acute porphyria has also stimulated a new interest in its pathogenesis. The clinical features of 50 cases of acute porphyria have therefore been summarized in the light of this work, and an attempt has been made to assess aetiological factors, including the genetic factor, and the mechanisms involved in the production of symptoms and signs. The clinical manifestations of the disease are so varied that special stress has been laid on the presenting symptoms and on diagnosis. Another aspect of practical importance to the general physician is the role which barbiturates may play in inducing and perpetuating attacks. It has been recognized that their use is contraindicated in a patient with the disease, but it has not hitherto been known whether prolonged administration of barbiturates to a normal person, or even to an apparently normal relative of a patient with the disease, might eventually

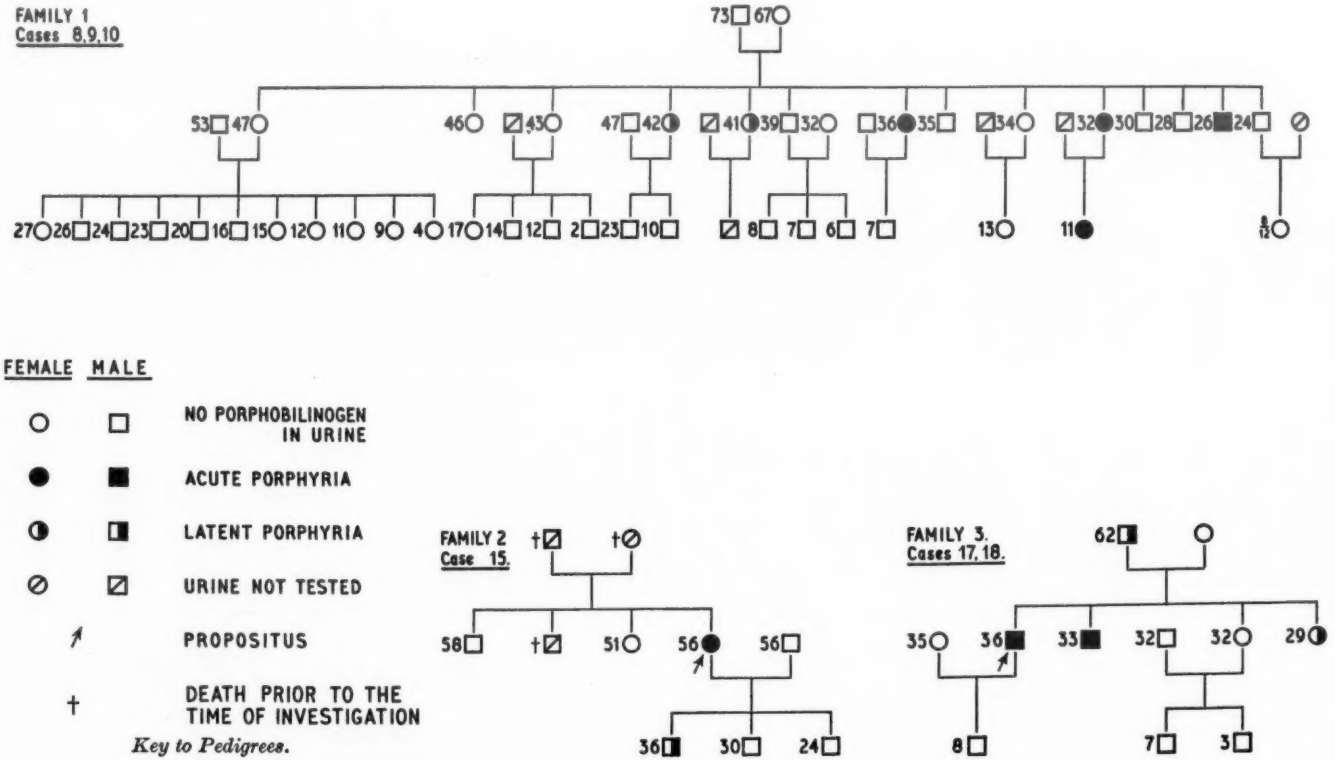
[1] Received May 6, 1958. [2] Present address.

precipitate an attack. Various forms of treatment have been advocated for acute porphyria, but the rarity of the disease and its tendency to natural remission make evaluation difficult. The study of these 50 cases has provided an opportunity for a critical appraisal of treatment.

Aetiology

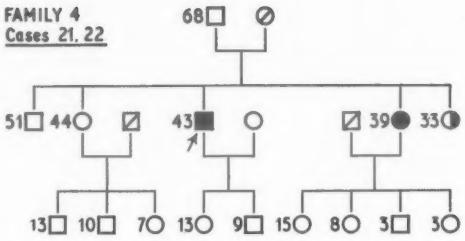
1. *The genetic factor.* The first observation that acute porphyria occurred in members of the same family was made by Barker and Estes (1912). Günther (1922) also noted a hereditary tendency in the disease, but it was Waldenström (1937) who firmly established its hereditary nature. Gates (1946) reviewed Waldenström's data, and considered that the disease was inherited as an irregular dominant character. In the present series of 50 cases at least 19 patients had one or more relatives with the active or latent condition. It was possible to study only 11 families in detail; the pedigrees are shown on pages 185 to 187. Latent porphyria was accepted as present if porphobilinogen was found in the urine on at least one occasion, and nine instances were revealed by investigation of patients' relatives. Specimens were tested as a routine by the methods of Watson and Schwartz (1941) and Vahlquist (1939). When a doubtful positive result was obtained, about 0·5 to 1 litre of urine was concentrated, and any porphobilinogen present was identified by paper chromatography (Westall, 1952; Cookson and Rimington, 1954). Concentrates of normal urine treated in this way did not contain detectable porphobilinogen. This method proved helpful in identifying three patients with latent porphyria who were excreting small quantities of porphobilinogen. It should be noted, however, that out of 18 patients with previously active porphyria whose urine was tested in a state of remission, five had ceased to excrete porphobilinogen. Moreover, one child under investigation did not excrete porphobilinogen at the age of eight years, but did so at 11 years. Thus the absence of porphobilinogen in the urine of a relative does not rule out the possession of the trait.

The findings in this series confirm those of Waldenström (1937, 1956). In four families the condition was found in more than one generation, and was apparently transmitted directly from a parent to one or more of the offspring. In another family, in which it was not possible to test the parents, two half-sibs with unrelated fathers were found to be affected. Thus a single gene would seem sufficient for the manifestation of the disease. There was no evidence of increased parental consanguinity. This familial distribution is consistent with the hypothesis that the condition is inherited as a Mendelian dominant character: that is, the persons affected are heterozygous for an abnormal gene. In two families, however, in which more than one of a group of sibs were affected, it was not possible to detect porphobilinogen in the urine of either of the parents. It must therefore be assumed that there is considerable variation in the degree of the expression of the character, and that in one family all grades can be found, from the acute case, through latent porphyria, to the apparently normal subject who excretes no porphobilinogen. It is possible that some of the latter



Key to Pedigrees.

Numbers against symbols indicate age at the time of investigation of the family.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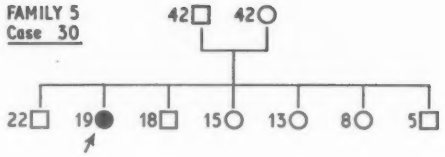
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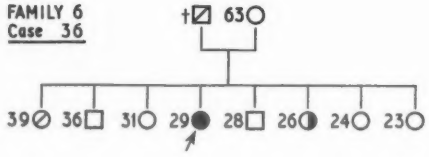
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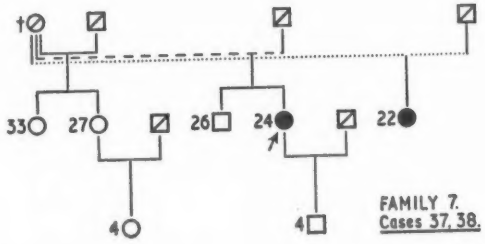
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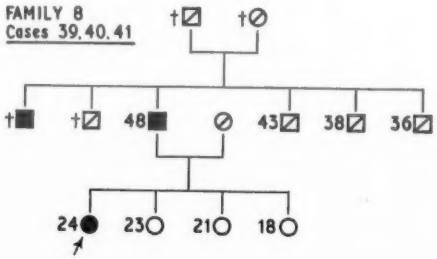
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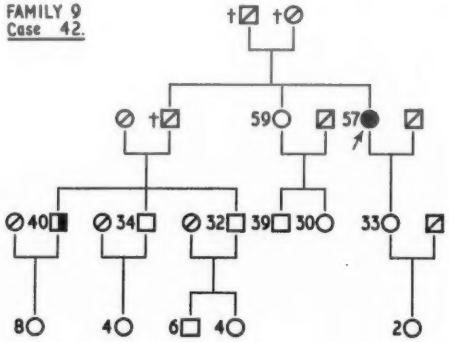
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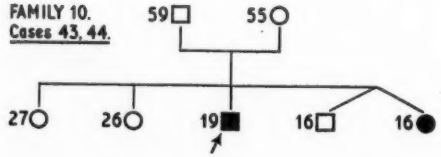
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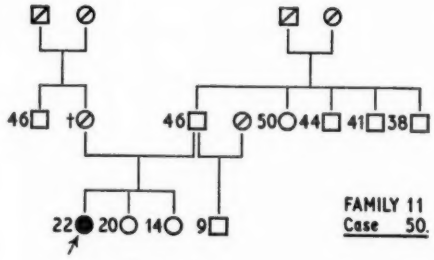
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group might begin to excrete porphobilinogen if suitably provoked. In only two families were there a parent and a child who both had the active disease. This is not altogether surprising, because if a gene produces a severe and lethal illness variable in its manifestations, those with the milder form of the affection are more likely to survive to adult life. The apparently sporadic occurrence of the disease in two families might be attributed to mutation, but it is probable that, in the majority of instances in which an affected child has apparently normal parents, one or other of the parents is heterozygous for the gene.

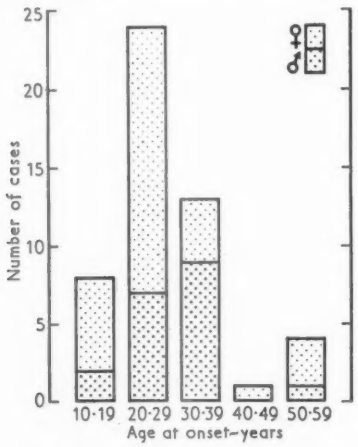


FIG. 1. Age at onset of symptoms.

From a study of these families it can be said that approximately 25 per cent. of the sibs of a patient may be expected to have porphobilinogen in the urine, and a high proportion of these are liable to have an acute attack. Furthermore, about one in four of the children of persons who excrete porphobilinogen may be expected to become similarly affected. If it is true that affected subjects are heterozygous for an abnormal gene, then two out of four children of parents, only one of whom is affected, should carry the abnormal gene. Thus half of those carrying the gene may not excrete porphobilinogen.

2. *Age and sex.* The most frequent age at onset (Fig. 1) in this series was the third decade in women and the fourth decade in men. The youngest patient was a girl of 11 years. In two of the five cases in which the onset took place after the age of 40 a history of prolonged administration of barbiturates was obtained. It is possible that a relationship exists between the ages at onset in sibs. Thus two patients, brothers, both had their first symptoms at the age of 30. A brother and sister started symptoms at 35 and 36 years respectively. Two sisters had their first attack at 23. Two brothers had the commencement of symptoms at 29 and 31 years respectively.

Priestley (1894) drew attention to the preponderance of female subjects with porphyria, and Garrod and Hopkins (1896) found that the majority of cases of 'sulphonal haematoporphyria' were women. Subsequent studies (for example,

Waldenström, 1937) have confirmed these impressions. In the present series there were 31 female and 19 male sufferers (62 per cent. and 38 per cent.). It is questionable whether this sex incidence is genetically determined, or whether secondary precipitating causes, such as pregnancy or barbiturate intoxication, predispose to the sex difference. The disease is no less severe in men, and of 12 deaths four were in male patients.

3. *Precipitating factors.* (1) *Barbiturates.* Since the introduction of the barbiturates into clinical medicine in 1903 there have been conflicting reports on their possible relation to human acute porphyria. Dobrschansky (1906) described a typical case of acute porphyria, without paralysis, occurring in a patient after prolonged administration of barbitone. Haxthausen (1927) reported the development of skin photosensitivity and the presence of excessive amounts of porphyrins in the urine of an epileptic who had been taking phenobarbitone for some time. Eliaser and Kondo (1942), Denny-Brown and Sciarra (1945), Prunty (1946), Jørgensen and With (1947), Macleod and Grant (1953), and Whittaker and Whitehead (1956) have all described deterioration in the clinical state of patients, with the development of severe or even fatal paralysis, after the administration of certain barbiturates, among which were phenobarbitone and pentobarbitone ('nembutal'). Waldenström (1939, 1940) was convinced that barbiturates may precipitate attacks in cases of latent porphyria, and that they seriously affect the prognosis. On the other hand, Günther (1922), Turner (1938), and Discombe and D'Silva (1945) failed to find any relation between barbiturates and acute porphyria. Information as to the relation of barbiturates to normal human porphyrin metabolism has been obtained from observations on the urinary porphyrin excretion in cases of barbiturate poisoning. Rosendorff (1910), Sowden (1910), MacLean (1912), and With (1957) found no abnormal porphyrinuria in patients who had ingested single large doses of barbiturate; Rommel (1912) observed dark-red urine in a patient who had taken 25 g. of barbitone. A study of the cases in the present series suggests two types of relationship between barbiturates and acute porphyria.

(i) If barbiturates are given over a prolonged period to a person with the genetic defect they may precipitate an attack. The evidence for this hypothesis is based on three cases in the present series in which barbiturates, mainly phenobarbitone, were given for periods of 18 months to two years. Among the presenting symptoms were drowsiness and loss of memory, incoherence and repetitiveness of speech, convulsions, hysteria-like behaviour, and depression. These symptoms recall the description by Fraser, Isbell, Eisenman, Wikler, and Pescor (1954) of chronic barbiturate intoxication or the sudden withdrawal of barbiturates. In each of these three cases the main symptoms and signs disappeared after the cessation of the drug, and there has been no recurrence for several years. Moreover, evidence has been obtained that the genetic abnormality exists in this type of case. Thus one of the three patients still passed porphobilinogen three years after the cessation of barbiturates, and the son of another has latent porphyria. It is also noteworthy that two of the patients were 56 and 59 years old respectively, and had suffered no previous symptoms.

It seems probable that prolonged ingestion of barbiturates may precipitate an attack of acute porphyria where the latent trait exists, and in such cases the clinical manifestations resemble those of chronic barbiturate intoxication.

(ii) There may be an association between the administration of barbiturates during an attack and the onset of paralysis. The evidence for this hypothesis is summarized in Fig. 2. Seventy-seven per cent. of patients with paralysis or paresis (24 out of 31) had been given barbiturates, while 35 per cent. of those without paralysis or paresis (six out of 17) had taken barbiturates. This difference is highly significant ($P<0{\cdot}01$). Of the seven patients with paralysis who

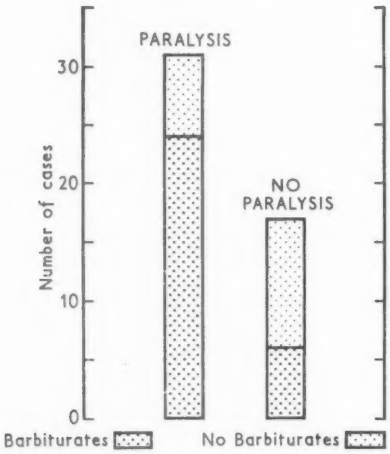


FIG. 2. The relationship between barbiturate administration and the onset of paralysis in 48 patients with acute intermittent porphyria. In two cases, not included in the analysis, it was not certain whether barbiturates had been given.

had not been given barbiturates, five had only mild neurological involvement, but one patient died with general weakness and bronchopneumonia after a prolonged smouldering course, and another had quite severe nerve involvement, including signs in the pyramidal tract. The most severely afflicted patients were in the group with paralysis and a history of barbiturate administration. In all of four patients to whom quinalbarbitone ('seconal') was given a quadriplegia ensued, and two of these patients died. It has been shown that some barbiturates have an effect in disturbing the porphyrin metabolism of rabbits, and that those with allyl groups, such as quinalbarbitone, are especially effective (Goldberg, 1954 *a*).

(2) *Menstruation and pregnancy.* Waldenström (1937) noted an apparent relation of the onset of clinical symptoms to menstruation. In the present series the beginning of an attack was closely associated with a menstrual period in seven women, and in these women the periods were generally delayed. The incidence of this association is not significantly greater than could be accounted

for by chance. Six other women had amenorrhoea, but this is a frequent accompaniment of debilitating disease, and one woman also had tuberculous endometritis. The occurrence of the disease in male subjects, in girls before puberty (two cases), and in post-menopausal women, shows that any association between menstruation and clinical symptoms, if present, is not a primary one.

Six cases showed an association with pregnancy. In three patients attacks began five days, 14 days, and 14 days respectively after the birth of a child. Three other women started to have symptoms in the very early weeks of pregnancy, and two of them died shortly after its termination. On the other hand,

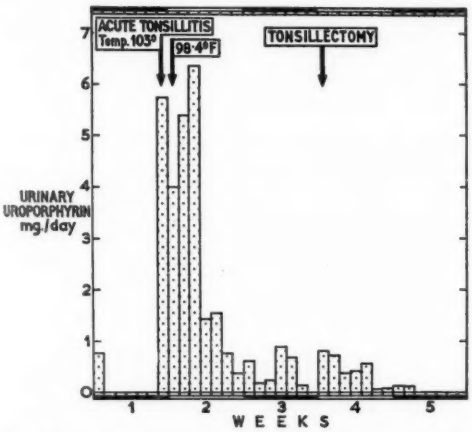


FIG. 3. The influence of infection on porphobilinogen excretion (expressed as uroporphyrin) in a woman aged 23 with acute porphyria.

there are several examples of normal pregnancies occurring in cases of acute porphyria, and some observers have reported marked improvement during pregnancy (Rawlings, 1950; Freedman, Yeagley, and Brooks, 1952). Thus no dogmatic statement can be made on the relationship between pregnancy and porphyria. In some cases pregnancy may be completed with impunity, but in others it may gravely and sometimes fatally overtax the patient.

(3) *Infection.* In the present survey there are many examples of the role of infection in precipitating or aggravating an attack. This is not surprising, since in other metabolic diseases, for example diabetes mellitus and Addison's disease, infection may play a similar role. Examples of acute tonsillitis precipitating an attack have been given by Waldenström (1937) and Denny-Brown and Sciarra (1945). This finding has been confirmed in five cases of the present series. In one patient the effect of the throat infection and tonsillectomy on porphobilinogen excretion has been recorded (Fig. 3). This woman had suffered two attacks, each associated with acute tonsillitis. She has had no further attacks since tonsillectomy four years ago. In another patient urinary infections repeatedly preceded further attacks, confirming the experience of Discombe and D'Silva (1945) and Abrahams, Gavey, and Maclagan (1947). Skin infection appeared to

be a precipitating or aggravating factor in three cases. Herpes zoster occurred in one case just before an attack. Vannotti (1954) has described herpes zoster, in the distribution of the ilio-inguinal nerve, recurring with each attack in a case of acute porphyria. Tuberculous endometritis was associated with an attack in one case. It was not known whether this infection precipitated the attack, but the patient has had no further attacks for two years after treatment of the endometritis.

(4) *Other factors.* In one patient exacerbations of the disease were preceded by bouts of alcoholic excess. In another patient attacks began on several occasions when he travelled by air or sea.

Clinical Features

Presenting symptoms

The main presenting symptoms are summarized in Fig. 4. Abdominal pain, either alone or associated with constipation, vomiting, or more rarely diarrhoea,

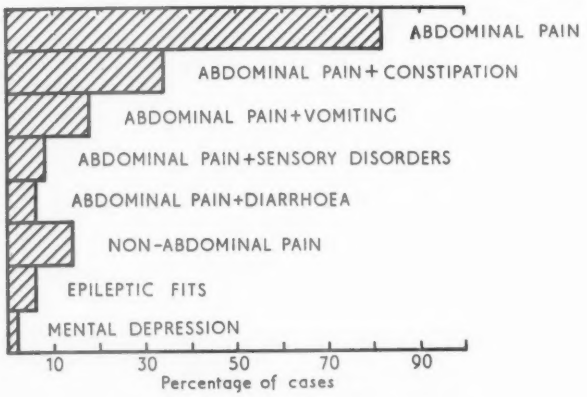


FIG. 4. Incidence of presenting symptoms.

was the most common complaint. This is in agreement with Günther's diagnostic triad of abdominal pain, vomiting, and constipation (1922). In 22 per cent. of cases, however, neurological or psychological symptoms were predominant, and the majority of these patients (nine out of 11) did not complain of abdominal pain. In a few cases (8 per cent.) there was a combination of abdominal pain and disorders of sensation, for example paraesthesiae or pains in the limbs. Three patients (6 per cent.) presented epileptic fits. Many patients had psychological symptoms on admission, but only one had such symptoms (mental depression and hysteria) as the presenting feature.

The incidence of symptoms and signs throughout the course of the disease is shown in Figs. 5 and 6.

Gastrointestinal features. Abdominal pain was predominantly colicky in nature, but there were periods lasting several hours, or even days, when it was constantly present. It was experienced in any part of the abdomen, but mainly

in the epigastrium and right iliac fossa; in some cases it extended over the whole abdomen. It was characteristically very severe and described as 'deep down', and usually caused great distress. All the patients who complained of abdominal pain, and who were examined by the author, had some abdominal tenderness. This was usually much less in degree than the severity of the pain

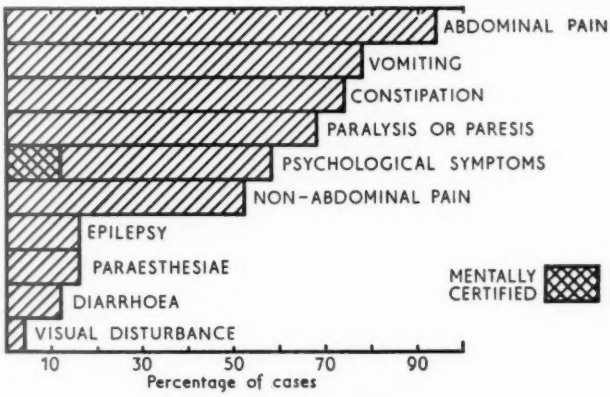


FIG. 5. Incidence of symptoms.

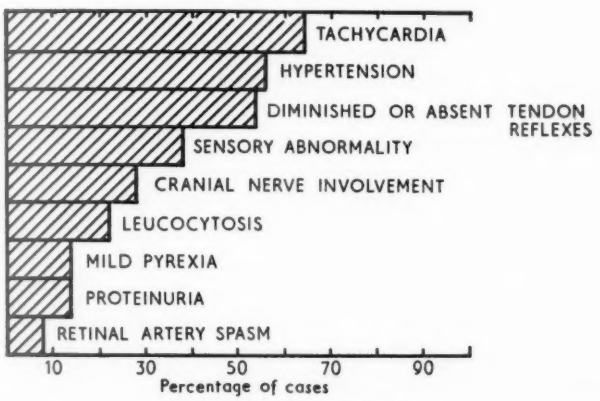


FIG. 6. Incidence of signs.

would have led one to expect, but except in two cases there was no muscular rigidity; in one patient the rigid abdomen was like that of a perforated duodenal ulcer, and in another there was localized rigidity in the right iliac fossa. Vomiting, sometimes accompanied by constipation, was associated with the abdominal pain in a large number of cases. Vomiting was usually preceded by abdominal pain, but in one case it occurred without this symptom. Six patients had diarrhoea as well as vomiting; one was initially sent to a fever hospital with a diagnosis of gastroenteritis. The occurrence of diarrhoea in acute porphyria has been noted in the past (Garrod and Hopkins, 1896; Günther, 1922; van den

Bergh, Dellaert, Grotepass, Nyssen, and van Bogaert, 1937). Waldenström (1937) described three cases of porphyria with an irritable colon ('mucous colitis'), a condition present in one case of the present series. Rectal examination was negative in those cases in which it was carried out, except for one instance of rectal tenderness. In all cases of some severity there was loss of weight during the attack.

Neurological features. 1. *Motor disturbance.* Paralysis or paresis of limb muscles occurred in 34 cases, varying in extent from weakness of a pair of limbs to complete quadriplegia. There was paresis of only the upper limbs in one case, paresis of only the lower limbs in five cases, and quadriplegia or quadriparesis in 28 cases. In the majority of patients paralysis was of lower motor neurone type; but in five patients extensor plantar responses were obtained, and in one of these there was muscular rigidity of the lower limbs, ankle clonus, and increased tendon reflexes. Upper as well as lower motor neurone lesions were described by Melkersson (1926) and Waldenström (1937). In 27 of the 34 patients with paralysis or paresis there were diminished or absent tendon reflexes, and in many cases there was marked muscular wasting. There was a predilection for the extensor muscles of the wrists and fingers, but there was no definite pattern of ascending paralysis of the Landry type. All cases of motor disturbance were bilateral, but usually unequally so. In severe cases the muscles of the trunk were also affected. Half of the 28 patients with paresis or paralysis of all four limbs had involvement of cranial nerves, for example diplopia, dysphagia, dysarthria, aphonia, or facial palsy; in three cases there was a partial and temporary loss of vision, lasting no longer than two days. Incontinence of urine occurred in six cases, and retention of urine in one. Incontinence of faeces occurred in one case. Five patients had respiratory paralysis due to involvement of the diaphragm or intercostal muscles, or both.

2. *Sensory disturbance.* Nineteen patients had impairment of sensation—analgesia, hypalgesia, hyperaesthesia, loss of joint and vibration sense, or complete sensory loss. The site of impairment was in the limbs, especially the lower limbs, in 18 cases; in four of these there was also impairment of sensation in the head or trunk. One patient had hypalgesia confined to the 'bathing-trunk' area. All but two of these 19 patients had muscular paralysis or paresis, which preceded the sensory loss. No sensory disorder was observed in 15 patients with muscular paralysis or paresis. Pain, probably of neurogenic origin, occurred in sites other than the abdomen. This observation has been made repeatedly since the earliest references by Ranking and Pardington (1890) and Harley (1890). In 26 cases pain was felt in the limbs, usually the legs, in the head and neck, in the large joints such as the shoulder and knee, in the lumbar region, or in the anterior chest region. In all except two cases the pain in these regions was accompanied by abdominal pain. One patient had nystagmus and cerebellar ataxia.

3. *Epilepsy.* The association of epileptiform seizures with acute porphyria was noted early in the history of the disease (Campbell, 1898; Brown and Williams, 1909). In the present series eight patients had epileptic fits. In seven

cases the fits were generalized; in one case they began in the left arm, passed to the left leg, and then became generalized. Hypertension was present in six of these cases, but was of a severe degree in only three. A history of previous barbiturate ingestion was obtained in only three patients, but in three others barbiturates were given to control the fits, and were associated with deterioration in the general condition. In one patient the fits continued until the barbiturates were stopped. Electroencephalograms were obtained from four of the patients with fits. Two were normal; one was abnormal, but its pattern was consistent with the stuporose condition of the patient; the fourth showed a mild dysrhythmia.

An electroencephalogram was obtained in one patient who did not have fits, and was reported as follows: 'Slightly abnormal. Confused, choppy type, with alpha waves and fast rhythm, and enough waves of 5–7 cycles/sec. to make it abnormal.' Berlin and Cotton (1950) and Perrault, Klotz, Canivet, and Caroit (1953) reported abnormal encephalograms in their patients. The former workers also noted low-voltage waves of five to seven cycles per second.

4. *Mental symptoms.* Twenty-nine sufferers had mental symptoms, and have been arbitrarily classified into three grades: (1) Depressed, nervous, hysterical, lacrymose, or 'peculiar' (14 cases). In one woman mental depression was the presenting symptom, and she was initially treated as an out-patient in a hospital for mental diseases. (2) Confused, hallucinated, disorientated, or with personality change (nine cases). (3) Legally certified (six cases).

Cardiovascular findings. Thirty-two patients had tachycardia during the acute phase of the disease. In most of these patients the pulse rate was 110 to 120, but in a few it rose to 150 or 160 per minute. The pulse rate was found to be a good index of the activity of the disease, as observed by Waldenström (1937). In a few patients extrasystoles or pulsus bigeminus were noted during a severe phase. Normal rhythm was re-established when the patient improved. Twenty-seven patients had transient hypertension (a systolic pressure of 150 or more and a diastolic pressure of 95 or more). The blood-pressure always returned to normal levels if the patient recovered. In some cases there was marked hypertension: one patient had a Grade II retinopathy (Keith, Wagener, and Barker, 1939) with a blood-pressure of 180/126; the fundus returned to normal when the blood-pressure became normal. Another patient had papilloedema and fits associated with hypertension. One woman was seen on account of 'essential hypertension', and a quinalbarbitone sedation test was given on two occasions, after which her condition rapidly deteriorated, and she died. One patient developed hypertension in the final attack, but not in the previous ones. Another developed hypotension (blood-pressure 70/54) at one phase of her condition. Hypertension in acute porphyria was first described by Melkersson (1926), but Bostroem (1920) recorded a blood-pressure of 95/30 in one case, and a diagnosis of essential hypertension was made in another case by Saint, Curnow, Paton, and Stokes (1954). Retinal artery spasm was seen in four cases of the present series.

Electrocardiograms were obtained in nine cases. Five were normal; in the

other four cases the following features were found: P2 was sharply pointed, and there were prominent atrial T waves (Ta), giving PQ depression and accompanied by ST depression in two cases. These findings suggest atrial damage, strain, or hypertrophy, possibly related to respiratory embarrassment. On the other hand, in one case, in which at autopsy right atrial dilatation and pulmonary collapse were present, these abnormalities were not present. Low-voltage T waves were found in three cases, suggesting generalized myocardial damage. The serum-potassium level in these cases was never low enough to account for these changes. There was some cardiac rotation in each of the four cases—clockwise in two, anti-clockwise in the remainder—possibly related to right heart strain and hypertension respectively. The electrocardiograms of the three patients who recovered reverted to normal. Similar electrocardiographic findings have been reported by other workers. Thus Berlin and Cotton (1950) found PQ depression in one case; Eliaser and Kondo (1942) found marked elevation of the ST segment, which they attributed to coronary arterial spasm. Degenerative changes of the myocardium have been described by Saint, Curnow, Paton, and Stokes (1954).

Dermatological findings. No patient had frank photosensitivity of the skin. One woman had a slight vesicular eruption on the cheeks and the bridge of the nose at the beginning of her illness; the lesions healed, with subsequent pigmentation of the facial skin. Eight patients showed a darkening of the exposed areas of the skin, which returned to a normal colour if the patient recovered. Waldenström found skin pigmentation in several of his cases, while Vannotti (1954) described 'mild cutaneous lesions of a vesicular nature'.

Temperature. Seven patients had an intermittent low-grade pyrexia (99° to 100·6° F) without obvious infection.

Clinical Pathology

Haematological findings. Haemoglobin determinations were recorded in 27 cases, and showed a mean of 14·7 g. per 100 ml. (range 11·8 g. to 17·3 g.), which is within normal limits. The erythrocyte sedimentation rate was recorded in 16 cases by the Westergren or Wintrobe methods. In 11 patients normal values were obtained. In five patients there were slightly elevated readings by the Westergren method (16 to 20 mm. in one hour). In 28 cases the leucocyte counts during the active phase were between 4,000 and 10,000 per cu. mm. A leucocytosis of more than 12,000 per cu. mm. was found in 11 cases, and was associated with either infection or epileptic fits.

Renal findings. Traces of protein were found in the urine in 12 cases, in four of which there were also a few granular casts. Such findings have been noted by many observers, for example, Garrod and Hopkins (1896) Günther (1911, 1922), Grund (1919), and Melkersson (1926). Van den Bergh, Dellaert, Grotepass, Nyssen, and van Bogaert (1937) and Harbitz (1924) even described the association of subacute and chronic nephritis respectively, while Stern (1894), Denny-Brown and Sciarra (1945), and Prunty (1949) found renal tubular nephrosis at autopsy in their patients. In no case of the present series was there

evidence of such serious renal disease. The blood urea was increased in three patients, but in each instance probably indicated an extrarenal type of uraemia due to excessive vomiting.

The cerebrospinal fluid was normal in respect of protein, sugar, chloride, and cell content, in all of the 11 cases tested. In one case the cerebrospinal fluid was tested for porphobilinogen and found to be negative.

Pyruvate-tolerance test. Only one case out of two tested was frankly abnormal. The blood-pyruvate level of this patient was 2·2 mg. per 100 ml. 90 minutes after the ingestion of glucose. The normal upper limit of blood pyruvate after 90 minutes is 1·34 mg. per 100 ml. (Joiner, McArdle, and Thompson, 1950).

Serum electrolytes. Abnormalities were found in six of eight cases investigated. Sodium and chloride levels were diminished in two cases. In three others the chlorides were somewhat diminished, while in another patient there was a hypochloraemia associated with a hypokalaemia and alkalosis. In each of these cases excessive vomiting had taken place. Vannotti (1954) considered similar electrolyte changes in his patients to be due to vomiting, but Prunty (1949) suggested that the pathological lesions he found in the renal tubules might have been the cause of the diminished plasma-sodium and plasma-chloride levels of his patient.

Empirical liver function tests were recorded in 20 cases. They were performed in different laboratories by different workers, but the following conclusions may be drawn. In the majority of cases no abnormality was detected. The alkaline-phosphatase levels in two patients studied during a severe attack were raised. Thymol turbidity was increased in one active case, and the thymol flocculation test was grossly abnormal in another. Cephalin flocculation was repeatedly abnormal in one patient, who was an alcoholic.

Creatinuria. Creatine (50 mg. to 700 mg. in 24 hours) was consistently present in the urine of one patient, with severe muscle wasting, in the acute phase of the disease. Vannotti (1954) has recorded creatinuria in a rare form of acute porphyria which he called 'myoporphyria', and in which muscular atrophy and decolorization were present.

Morbid Anatomy

Post-mortem examinations were carried out in six cases. The findings were non-specific. Terminal respiratory infection was found in three, and pulmonary oedema, due to left ventricular cardiac failure, had occurred in one case. In another case there were small intrapulmonary haemorrhages and areas of collapse, secondary to respiratory paralysis; there was also a small pericardial effusion of about 15 ml. of slightly cloudy fluid, but no pericarditis; the right auricle was dilated; on microscopic examination there was fine patchy atheroma of the coronary arteries, and a little oedema of the left ventricular myocardium. In one case there was fatty degeneration of the liver and gastric petechial haemorrhages. Gibson and Goldberg (1956) have reported on the neuropathology of acute porphyria in five cases, four of which belong to the present series. and Drury (1956) has described a biopsy of a dorsal interosseus nerve of the foot.

The neuropathological findings are referred to in the discussion on pathogenesis.

Chemical Pathology of Post-Mortem Tissues

Analysis of post-mortem tissues for porphyrins and porphobilinogen was carried out in six cases of acute porphyria, and in two control patients who did not have porphyria, by the methods described by Goldberg (1954*a*). The results are summarized in Table I. In the patients with acute porphyria, all the samples of liver and kidney examined contained porphobilinogen, and the liver contained some uroporphyrin in the cases in which this substance was looked for. In contrast, the control tissues contained neither porphobilinogen nor uroporphyrin. The liver, bone-marrow, and spleen, in patients who died from porphyria, did not have significantly higher concentrations of coproporphyrin and protoporphyrin than the tissues of control patients. The kidney of one patient had raised concentrations of coproporphyrin and protoporphyrin. The presence of porphobilinogen in the liver and kidney in these cases corroborates the findings of Prunty (1945), Gray (1950), and Schmid, Schwartz, and Watson (1954).

Diagnosis

Acute porphyria has been well named 'the little simulator'. A definite diagnosis rests on the presence of porphobilinogen in the urine, but it is most important to realize that this comparatively rare disease may present symptoms suggestive of an acute abdominal condition, a psychosis or psychoneurosis, a peripheral neuritis, or an epilepsy of unknown causation. In the present series six patients underwent laparotomy because of their symptoms. Acute porphyria may mimic any acute abdominal emergency. One patient developed abdominal symptoms four months after the birth of her child, and a diagnosis of postpartum salpingitis was made. Other incorrect diagnoses included poliomyelitis, acute rheumatism, and post-herpetic encephalitis. On the other hand, the coexistence of a second condition, unrelated to porphyria, may complicate the diagnosis. One patient was shown to have a gastric ulcer in addition to acute porphyria.

Course and Prognosis

In these 50 cases the course of acute porphyria was variable. A few patients merely felt intermittent and occasional abdominal pain; others had explosive, fatal attacks, which lasted from 10 days to 10 weeks. In the majority of cases the course lay between these extremes, attacks recurring for months or years. A 'step-ladder' pattern of increasing severity was seen in two cases. In both of these cases three attacks occurred over a period of months, each one more severe than the last, until the final paralytic and fatal attack took place. In two cases the patient's condition deteriorated throughout pregnancy, until death occurred shortly after the birth of the child. Many patients recovered

TABLE I

Chemical Analysis of Post-Mortem Tissues

(Results expressed as μg. per g. of wet tissue)

Case	*Liver*				*Kidney*				*Bone-marrow*				*Spleen*			
	Pbg	*Uro*	*Copro*	*Proto*	*Pbg*	*Uro*	*Copro*	*Proto*	*Pbg*	*Uro*	*Copro*	*Proto*	*Pbg*	*Uro*	*Copro*	*Proto*
Control I . . . Aged 50 years. Myocardial infarction	0	0	1·1	1·0	0	0	0·3	1·9	0	0	1·1	0·9	0	0	0·8	0·7
Control II . . . Aged 78 years. Cardiac failure. Pneumonia	0	0	0·2	1·3	0	0	0·3	0·7	0	0	0·6	0·9	0	0	0·4	0·5
Patients																
No. 1 . . .	50	1·9	1·8	3·3	..	..	..	..	0	0	0·2	0·8	0	0	0·3	0·8
No. 2 . . .	36	8·5	1·2	0·6	..	..	..	..	0	0	0·2	0·2	0	0	0·2	0·2
No. 3 . . .	19	..	..	..	51	..	..	..	0	..	..	..	0	..	..	..
No. 23 . . .	18	9·6	0·9	0·8	..	..	..	..	..	..	..	..	..	..	..	..
No. 24 . . .	17	..	0·4	0·7	..	..	..	..	0	..	..	..	..	..	..	..
No. 43* . . .	31	2·9	0·7	0·5	49	14	7·7	2·4	0	0	0·5	0·2	0	0	0·4	0·5

Pbg = porphobilinogen.
Uro = uroporphyrin.
Copro = coproporphyrin.
Proto = protoporphyrin.

* Heart, lung, spinal cord, skeletal muscle, thyroid, adrenal, and pancreas did not contain porphobilinogen.

quickly and completely. Some were left severely crippled, or even insane, after an attack. Complete restitution of physical and mental function was the rule in these patients, but in some cases this took four or five years. Two patients were mentally ill for several years, but both eventually returned to a normal state. Four others had marked wasting and weakness of musculature, but showed

TABLE II

Relation of Mortality to Age at Onset of the Disease

Age group (years)	*Number of cases*	*Number of fatal cases*	*Mortality (%)*
10–19	8	5	63
20–29	24	4	17
30–39	13	2	15
40–49	1	0	0
50–59	4	1	25
Total	50	12	24

TABLE III

Analysis of Deaths

Case number	*Sex*	*Age at onset (years)*	*Duration of illness*	*Precipitating cause of death*
1	F	23	1 year	General paralysis. Bronchopneumonia
2	F	52	4 weeks	General paralysis. Pulmonary oedema
3	F	29	19 months	End of pregnancy 10 days before death. Pneumonia; hypochloraemic alkalosis; extrarenal uraemia
5	F	24	6 months	General paresis. Respiratory paralysis
23	F	17	10 days	Respiratory paralysis
24	M	33	16 days	General paralysis
30	F	19	6 months	General paresis. Death two hours after premature birth of child
32	F	20	10 weeks	General paralysis
33	M	13	1 year	Respiratory paralysis
41	M	31	2 years	Respiratory paralysis
43	M	18	2 years	Bronchopneumonia. General paresis
48	F	15	16 months	Respiratory paralysis

remarkable recoveries. The death-rate in relation to age groups is recorded in Table II. The overall mortality is 24 per cent. within an observation period of five years. The 12 fatal cases are further analysed in Table III. It can be seen that the majority of patients who succumbed died from paralysis, with or without a terminal respiratory infection. In Case 3 there was also a profound electrolyte disturbance. The most dangerous decade for the patient with acute porphyria is the second, in which there was a mortality of 63 per cent. Patients in the third decade seemed more liable to relapse. The four patients above the age of 40 who survived their first attack have not relapsed for several years. The impression was also gained from five other cases that a patient in any age group who survives a profound and crippling attack is unlikely to have a major relapse, although minor relapses may occur.

Treatment

Prophylaxis. There is at present no specific treatment for acute porphyria, and it is therefore especially important to prevent the onset of acute attacks. Whenever an active case is discovered it becomes a duty to test the urine of the patient's relatives for the presence of porphobilinogen. In this way the family doctor can identify cases of latent porphyria, and so avoid the dangers of the delayed diagnosis of an acute attack. On the other hand, there is no guarantee that a relative without porphobilinogenuria does not have the genetic defect, since, as has already been pointed out, persons heterozygous for the abnormal gene may not excrete porphobilinogen in the urine. Furthermore, five out of 18 patients in the present series did not have porphobilinogen in the urine in states of remission. Hence no member of a family in which there is a known case should ever be given barbiturates. Several alternative hypnotics are now available.

In dealing with an established case in remission, care should be taken to avoid known precipitating factors, and infections should be treated swiftly. Tonsillectomy seemed to be a valuable preventive measure in one case. Advice on pregnancy may be asked, but no dogmatic answer can be given. The dangers must be explained, and if pregnancy ensues the obstetrician should be warned. If any surgical procedure becomes necessary, a barbiturate must not be used as an adjuvant to anaesthesia. Careful surveillance throughout the puerperium is necessary, since this period, especially the early part of it, is a treacherous one.

Treatment of an acute attack. Usually the patient is difficult to treat and to nurse. When gross psychological disturbance and severe abdominal pain are present, it is usually advantageous to place the patient in a side ward rather than in a general ward. If there are signs of paralysis an artificial respirator should be available. For the relief of pain pethidine or morphine is usually necessary; aspirin is not contra-indicated, but is usually too weak an analgesic. Chloral hydrate and paraldehyde are safe hypnotics. If excessive vomiting has occurred, the re-establishment and maintenance of salt and water balance are important. Infection should be sought and treated. Substantial elevations of temperature (more than 101° F), a leucocyte count of more than 12,000 per cu. mm. (in the absence of convulsions), or an erythrocyte sedimentation rate of more than 20 mm. in an hour, should give rise to the suspicion that infection exists. In many patients the correct diagnosis is overlooked for some time. The patient may begin to accept the statement that the very real pain she is suffering is due to 'nervousness' or even 'imagination', and in some cases this situation may in itself aggravate the mental state of the patient. For this reason it is a kindness to explain that the symptoms have been brought about by a definite disease. In one family a brother of two sibs with acute porphyria developed a hysterical equivalent of the disease, but had no porphobilinogenuria. This fear, which may be present in healthy relatives, should be noted. Where paralysis or paresis has occurred the limbs should be correctly maintained in positions

of function, and active physiotherapy should be started as soon as possible and continued until complete recovery has been attained.

The efficiency of any specific treatment is difficult to assess, since spontaneous remission and rapid improvement are so often encountered. In spite of this, it is of value to attempt an assessment of the various kinds of drug therapy used in these 50 cases. It is of historical interest to note that Urquhart (1898) suggested that suprarenal extract should be tried in cases of porphyria, since disease of the suprarenals had been recorded in this condition; and Campbell (1898) gave 'suprarenal tabloids' to a porphyria patient, without effect. Prunty (1949), however, found evidence of adrenal cortical hyperplasia in his patient. *Corticotrophin* was given to five patients of the present series. In three there was no obvious effect, but in the other two some improvement followed its administration. Corticotrophin was of use in those cases in which there was generalized weakness or depletion of salt and water, or both (Goldberg, Macdonald, and Rimington, 1952). Watson (1954) strongly advised that corticotrophin should be given as early as possible in the course of the disease. In two cases of the present series cortisone had no effect; in two others some improvement was associated with its administration.

In many cases of acute porphyria there is an apparent increase in sympathetic activity (hypertension, tachycardia, constipation), and a myasthenia-gravis-like picture has been described (Denny-Brown and Sciarra, 1945). It is not surprising, therefore, that *neostigmine* has been used in the treatment of this condition, in some cases with good effect (Waldenström, 1944; Berg, 1945; Gordin, 1948; Veflingstad, 1949; Oïgaard and Roos, 1953; Gillhespy and Smith, 1954), and in others without benefit (Ashby and Bulmer, 1950; Fawcett, 1954). Berg (1945) and Berlin and Cotton (1950) observed, by kymograph and X-ray examination respectively, an improvement in the peristaltic activity of the stomach and small intestine in cases of acute porphyria after the injection of neostigmine. In the present series neostigmine had no effect on the paralysis or pain in five cases, but relieved constipation and retention of urine in one case. Some patients with acute porphyria might be symptomatically helped by this drug, especially where there is a diminished action of smooth muscle. *Ganglion-blocking drugs* may be used to diminish hypertension. They will not alter the course of the disease, and may not relieve pain *pari passu* with the depression of hypertension. Wehrmacher (1952) has described the variable effects of tetraethyl ammonium chloride and tubocurarine chloride on pain in a case of acute porphyria. In the present series the following drugs were used without apparent benefit: intravenous calcium gluconate, diphenhydramine hydrochloride, tolazoline hydrochloride, propantheline bromide, and deoxycortone acetate. Thiamine and riboflavin were given orally or parenterally to several patients, but without benefit to any except one, who was an alcoholic. Melby, Street, and Watson (1956) have suggested that chlorpromazine hydrochloride is an effective remedy for the pain and psychoneurotic manifestations of the disease.

Treatment after a severe attack. It has been emphasized that complete recovery of physical and mental function may take several years. The physician should

therefore persist with physiotherapy and the correction of limb deformities. If mental symptoms continue, the patient's relatives should receive the comfort of a sanguine prognosis. Relapses may occur, although they are usually not severe. Steroid therapy should be started immediately.

Pathogenesis

Since the early descriptions of acute porphyria there has been speculation as to its pathogenesis and the mechanism of the causation of symptoms (Harley, 1890; Stokvis, 1895; Oswald, 1895; Barker and Estes, 1912; Snapper, 1922). Garrod (1923) considered that patients with congenital porphyria lacked an enzyme which was responsible for one of the stages in the conversion of blood pigment into bile pigment. Several authors claimed that porphyrins might influence isolated strips of animal intestine or uterus (Günther, 1922; Supniewski, 1927; Reitlinger and Klee, 1928; Simici, 1938; Vannotti, 1954). These pharmacological studies seemed convincing proof (Carrié, 1936) that the substances responsible for the clinical features of the disease were the porphyrins. Berg (1945) suggested that the porphyrins produced a block in neuromuscular transmission. Waldenström (1937, 1939), however, cast doubt on the view that symptoms were caused by porphyrins, but stressed the importance of vasospasm. He also suggested that certain pyridine derivatives, possibly formed from the excessive pyrroles, affected the nervous system. Lowry, Schmid, Hawkinson, Schwartz, and Watson (1950) suspected that porphobilinogen, or some closely related substance, was the cause of the clinical manifestations, while Denny-Brown and Sciarra (1945) considered that the pathological changes in the nervous system might be caused by an intermittent ischaemia, probably due to a circulating vasoconstrictor substance. Goldberg, Paton, and Thompson (1954) showed that purified porphyrins and porphobilinogen are pharmacologically inactive, and also produced evidence which rendered unlikely the suggestion that a circulating vasoconstrictor substance is present in acute porphyria. This evidence was greatly strengthened when an experimental porphyria was produced in rabbits, rats, and fowls by the non-hypnotic substance allyl-isopropylacetamide (Goldberg, 1953; Goldberg and Rimington, 1955). In this condition the animals excreted large amounts of porphobilinogen, yet showed no features similar to acute porphyria in man, apart from constipation and loss of weight. Furthermore, porphobilinogen, and not porphyrins, is the main excretion product in acute porphyria in man. This may explain the absence of gross photosensitivity of the skin in acute porphyria, since photosensitivity is found in other types of porphyria in which formed porphyrins are excreted. The darkening of the skin noted in several cases of the present series may be caused by the simultaneous excretion of δ-aminolaevulic acid (Granick and Schrieck, 1955), which has some slight photosensitizing action (Scott, 1955; Jarrett, Rimington, and Willoughby, 1956).

Although views on the origin of the clinical manifestations have, therefore, been contradictory, there has been increasing agreement that the liver is the site

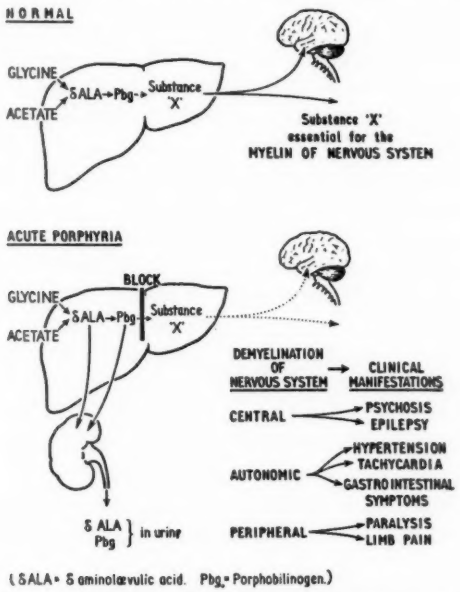
of the abnormal porphyrin metabolism. In 1945 Prunty found porphobilinogen in the liver of a case of acute porphyria. This finding was confirmed by Gray (1950) and Schmid, Schwartz, and Watson (1954). Goldberg (1955) showed that the porphobilinogen in the liver of a rat with experimental porphyria was made *in situ* and was not transported from an extrahepatic site. He also suggested that the results found in the experimental porphyria of the rat were applicable to acute porphyria in man, since in both states porphobilinogen is found in the same tissues, and the mechanism of the renal excretion of porphobilinogen is the same (Goldberg, 1954*b*). In 1956 Gibson and Goldberg confirmed the importance of primary demyelination in this disease. The general distribution of this pathological change throughout the nervous system suggested that the clinical features may be explained entirely on a neurogenic basis.

The neurological clinical manifestations can be explained on the basis of the neuropathological findings. Thus the demyelination of peripheral nerves, demonstrated *post mortem* or by biopsy, explains the limb paralysis. Lesions in the phrenic nerve were found in one patient who died with respiratory paralysis. In another patient, with both ataxia and nystagmus, foci of demyelination were found in the white matter of the cerebellum. Perivascular foci of demyelination were found *post mortem* in the cerebral white matter of four patients who showed mental changes during life, and it is significant that Spillane (1947) observed that cerebral demyelination, when it occurs in subacute combined degeneration of the cord, is usually found in patients who have had psychotic manifestations.

Gastrointestinal features are chiefly pain, constipation, vomiting, and diarrhoea. Intestinal spasms alternating with atonia and dilatation varying in location, but predominantly in the upper tract, have occasionally been observed at laparotomy (Vannotti, 1954), and have also been demonstrated both by intragastric balloon (Berg, 1945) and by radiography (Berlin and Cotton, 1950; Calvy and Dundon, 1952). It is suggested that these abnormalities may be due to lesions of the pre-ganglionic motor fibres that innervate the viscera. These fibres have their cell stations in the spinal cord and medulla. Retrograde degenerative changes have been found in these nuclei (Gibson and Goldberg, 1956). Demyelination of the vagus nerves, and of fibres of the sympathetic chain, was also noted in other cases. Berlin and Cotton (1950) have put forward a similar neurogenic hypothesis for the gastrointestinal features of this disease. They pointed out the similarity of the effects of porphyria and vagotomy upon gastrointestinal motility, and considered that the greater involvement of parasympathetic innervation in porphyria may be responsible for dilatation and atony as the predominant functional disturbance. Watson (1954) reported marked relief of abdominal pain in one case after bilateral splanchnicectomy.

Non-abdominal pain in the limbs and elsewhere may be due to damage to sensory fibres in the peripheral nerves. The changes in the posterior spinal root ganglia in the patients of Gibson and Goldberg (1956) were slight and inconstant, but such changes have been described by others (Bostroem, 1920; Mason, Courville, and Ziskind, 1933; Denny-Brown and Sciarra, 1945).

Hypertension and tachycardia. The sino-aortic regulation of blood-pressure and pulse rate is an important buffer mechanism. Pulsatile expansion of the carotid sinus and aorta stimulates the passage of impulses along the afferent pathways of the medullated carotid sinus and aortic nerves, which join the glossopharyngeal and vagus nerves respectively. They end in the reticular substance and the nucleus of the tractus solitarius, and are distributed to neighbouring vasomotor centres and also to the hypothalamic circulatory centres. It



(δALA = δ aminolævulic acid. Pbg = Porphobilinogen.)

FIG. 7. Hypothetical scheme of the pathogenesis of acute intermittent porphyria (see text).

is clear that interruption at any point in this pathway may block the buffer mechanism and give rise to hypertension and tachycardia. Changes in the vagus nerves, nucleus solitarius, dorsal vagal nucleus, and reticular substance have been observed in three cases (Gibson and Goldberg, 1956). Kezdi (1954) has investigated this buffer mechanism in a case of acute porphyria, by observing the effect on blood-pressure and pulse rate of stimulation of the carotid sinus by digital pressure or by block with procaine. He noted an absence of response in the active phases of the disease, and considered interference with this mechanism as a neurogenic cause of the hypertension and the tachycardia.

Thus it is possible to explain all the main clinical features of acute porphyria on a neurological basis. It is suggested that in this disease there is a fundamental disturbance of pyrrole-pigment metabolism in the liver. There is a related disturbance in the metabolism of the nervous system, of which demyelination is the pathological expression. The exact nature of the association between these two abnormalities is not yet clear. The recent elucidation of the porphyrin-like

structure of vitamin B_{12} (Bonnet, Cannon, Johnson, Sutherland, and Todd, 1955) may have some relevance, particularly when it is realized that demyelination takes place in subacute combined degeneration of the cord. This hypothesis is illustrated in Fig. 7. A substance 'X' has been assumed, of which porphobilinogen is a precursor, and which is essential for the nutrition of the myelin of the nervous system. A metabolic 'block' to the formation of this substance in the liver would lead to an excessive production of porphobilinogen and δ-aminolaevulic acid, and also give rise to demyelination. It is possible that a genetically determined deficiency in a specific enzyme, variable in the expression of its severity, might explain the 'block'. The intermittent nature of the disease might be related to the effect of other conditions, such as endocrine factors, infection, and barbiturates, on this abnormally sensitive pathway.

On this hypothesis the role of the barbiturates requires particular mention. They appear to be associated with the onset or the aggravation of the neurological phase of the disease, and they may precipitate an attack. Barbiturates have their hypnotic effect by inhibiting the oxidative mechanisms of brain tissue, and some of them, at least, affect pyrrole-pigment metabolism in animals (Goldberg, 1954 *a*). Barbiturates may produce their adverse effect in acute porphyria not only by inhibition of the formation of substance 'X', but also by a direct depression of the oxidation of brain tissue. To the physician acute porphyria represents a rare metabolic disease with diverse and unrelated manifestations. The varied clinical features, and the confusing pattern of chemical and histopathological findings, may be explained on this general hypothesis.

I am deeply grateful to the many physicians, biochemists, and pathologists who allowed me to study their patients, and whom it is not possible to name individually.

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Summary

1. The causation, natural history, and treatment of acute intermittent porphyria have been studied in 50 cases.

2. A genetic survey was carried out on 11 affected families. This was aided by the use of a paper-chromatographic method for the detection in the urine of trace amounts of porphobilinogen, the characteristic excretion product of acute porphyria. The survey confirmed the view that the disease is inherited as an irregular Mendelian dominant character. About one in four of the children of persons who excrete porphobilinogen may be expected to become similarly affected. Half of those carrying the abnormal gene may not excrete porphobilinogen, and five out of 18 subjects in states of remission did not have porphobilinogen in the urine.

3. Various conditions which apparently precipitated or aggravated attacks were studied. Increased susceptibility to attacks occurred during the first trimester of pregnancy, and in the few days immediately following delivery. Infections and barbiturates precipitated attacks. Barbiturates, when given over prolonged periods to persons genetically disposed to the disease, precipitated attacks; when they were given during the course of an attack the onset of paralysis was accelerated. Barbiturates which contained an allyl group appeared to be particularly dangerous.

4. The clinical features of the disease have been analysed. Most patients presented abdominal pain, accompanied by constipation, vomiting, or diarrhoea. Ten patients were first seen because of pain in sites other than the abdomen, epileptic fits, or mental depression. Thirty-four patients had muscular paralysis or paresis. In the majority of these cases the paralysis was of the lower-motor-neurone type, but five patients had signs of involvement of the pyramidal tract. Nineteen patients had some form of sensory disturbance. Twenty-nine patients had mental symptoms, and six were legally certified. Hypertension was found in 28 patients, and tachycardia was a good index of activity of the disease in 32 cases.

5. The age incidence was highest in the third decade in women, and in the fourth decade in men. The overall mortality for all age groups was 24 per cent. Prognosis was influenced by the age at onset of the disease. Young patients were more liable to the severest form of the disease, and more likely to relapse. A considerable variation was found in the rate of recovery from attacks. Some patients recovered quickly and completely. Others were left severely crippled, or even insane, after attacks. Complete restitution of physical and mental function occurred in these afflicted patients, but the recovery took up to five years in some cases.

6. The value of various forms of treatment was assessed. Prevention of attacks is of great importance, and no member of a family in which there is a known case should ever be given barbiturates. Steroid therapy should be instituted immediately an attack of any severity is diagnosed. Ganglion-blocking drugs may be used to diminish hypertension. Because of the associated vomiting, water and electrolyte balance are of great importance. Chlorpromazine hydrochloride may be of value for pain and psychoneurotic manifestations. The prevention and treatment of limb deformities are essential both during and after attacks.

7. It is suggested that in acute porphyria there is a disturbance of pyrrole-pigment metabolism in the nervous system, related to that which is known to exist in the liver. Demyelination is the pathological expression of this disturbance. The clinical features may be explained entirely on a neurogenic basis.

REFERENCES

Abrahams, A., Gavey, C. J., and Maclagan, N. F. (1947) *Brit. med. J.* **2**, 327.
Ashby, D. W., and Bulmer, E. (1950) Ibid. **2**, 248.
Barker, L. F., and Estes, W. L. (1912) *J. Amer. med. Ass.* **59**, 718.

Berg, M. (1945) *Arch. intern. Med.* **76**, 335.
Bergh, A. A. H. van den, Dellaert, R., Grotepass, W., Nyssen, R., and van Bogaert, L. (1937) *Ann. Méd.* **42**, 510.
Berlin, L., and Cotton, R. (1950) *Amer. J. dig. Dis.* **17**, 110.
Bonnet, R., Cannon, J. R., Johnson, A. W., Sutherland, I., and Todd, A. R. (1955) *Nature (Lond.)* **176**, 328.
Bostroem, A. (1920) *Zbl. ges. Neurol. Psychiat.* **56**, 181.
Brown, W. L., and Williams, H. O. (1909) *Lancet*, **1**, 1105.
Calvy, G. L., and Dundon, C. C. (1952) *Radiology*, **58**, 204.
Campbell, K. (1898) *J. ment. Sci.* **44**, 305.
Carrié, C. (1936) *Die Porphyrine*, p. 67. Leipzig.
Cookson, G. H., and Rimington, C. (1954) *Biochem. J.* **57**, 476.
Denny-Brown, D., and Sciarra, D. (1945) *Brain*, **68**, 1.
Discombe, G., and D'Silva, J. L. (1945) *Brit. med. J.* **2**, 491.
Dobrschansky, M. (1906) *Wien. med. Presse*, p. 2145.
Drury, R. A. B. (1956) *J. Path. Bact.* **71**, 511.
Eliaser, M., and Kondo, B. O. (1942) *Amer. Heart J.* **24**, 696.
Fawcett, J. W. (1954) *Lancet*, **1**, 1079.
Fraser, H. F., Isbell, H., Eisenman, A. J., Wikler, A., and Pescor, F. T. (1954) *A.M.A. Arch. intern. Med.* **94**, 34.
Freedman, A., Yeagley, J. D., and Brooks, J. B. (1952) *Ann. intern. Med.* **36**, 1111.
Garrod, A. E. (1923) *Inborn Errors of Metabolism*, 2nd ed. London.
—— and Hopkins, F. G. (1896) *J. Path. Bact.* **3**, 434.
Gates, R. R. (1946) *Human Genetics*, p. 530. New York.
Gibson, J. B., and Goldberg, A. (1956) *J. Path. Bact.* **71**, 495.
Gillhespy, R. O., and Smith, S. G. (1954) *Lancet*, **1**, 908.
Goldberg, A. (1953) 4th Congr. Europ. Soc. Haematology, Abstract, p. 27.
—— (1954 *a*) *Biochem. J.* **57**, 55.
—— (1954 *b*) *Lancet*, **2**, 1095.
—— (1955) *Biochem. J.* **59**, 37.
—— Macdonald, A. C., and Rimington, C. (1952) *Brit. med. J.* **2**, 1174.
—— Paton, W. D. M., and Thompson, J. W. (1954) *Brit. J. Pharmacol.* **9**, 91.
—— and Rimington, C. (1955) *Proc. roy. Soc. B*, **143**, 257.
Gordin, R. (1948) *Nord. Med.* **42**, 1432.
Granick, S., and Schrieck, H. G. V. (1955) *Proc. Soc. exp. Biol. (N.Y.)* **88**, 270.
Gray, C. H. (1950) *Arch. intern. Med.* **85**, 459.
Grund, G. (1919) *Zbl. inn. Med.* **40**, 810.
Günther, H. (1911) *Dtsch. Arch. klin. Med.* **105**, 89.
—— (1922) *Ergbn. allg. Path. path. Anat.* **20**, 608.
Harbitz, F. (1924) *Arch. intern. Med.* **33**, 632.
Harley, V. (1890) *Brit. med. J.* **2**, 1169.
Haxthausen, H. (1927) *Derm. Wschr.* **84**, 827.
Jarrett, A., Rimington, C., and Willoughby, D. A. (1956) *Lancet*, **1**, 125.
Joiner, C. L., McArdle, B., and Thompson, R. H. S. (1950) *Brain*, **73**, 431.
Jørgensen, J., and With, T. K. (1947) *Lancet*, **1**, 54.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939) *Amer. J. med. Sci.* **197**, 332.
Kezdi, P. (1954) *A.M.A. Arch. intern. Med.* **94**, 122.
Lowry, P. T., Schmid, R., Hawkinson, V. E., Schwartz, S., and Watson, C. J. (1950) *Bull. Univ. Minn. Hosp.* **22**, 97.
MacLean, I. C. (1912) *Lancet*, **1**, 647.
Macleod, J. G., and Grant, I. W. B. (1953) *Edinb. med. J.* **60**, 232.
Mason, R., Courville, C., and Ziskind, E. (1933) *Medicine (Baltimore)*, **12**, 355.
Melby., J. C., Street, J. P., and Watson, C. J. (1956) *J. Amer. med. Ass.* **162**, 174.
Melkersson, E. (1926) *Acta med. scand.* **63**, 153.
Oïgaard, H., and Roos, B. E. (1953) *Nord. Med.* **49**, 411.

Oswald, L. R. (1895) *Glasg. med. J.* **43**, 1.
Perrault, M., Klotz, B., Canivet, J., and Caroit, M. (1953) *Bull. Soc. méd. Hôp. Paris*, **30–31**, 1048.
Priestley, J. (1894) *Med. Chron.* N.S. **1**, 429.
Prunty, F. T. G. (1945) *Biochem. J.* **39**, 446.
—— (1946) *Arch. intern. Med.* **77**, 623.
—— (1949) *J. clin. Invest.* **28**, 690.
Ranking, J. E., and Pardington, G. L. (1890) *Lancet*, **2**, 607.
Rawlings, E. E. (1950) *Brit. med. J.* **1**, 549.
Reitlinger, K., and Klee, P. (1928) *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.* **127**, 227.
Rommel (1912) *Charité-Ann.* **36**, 62.
Rosendorff, W. (1910) *Berl. klin. Wschr.* **47**, i, 934.
Saint, E. G., Curnow, D., Paton, R., and Stokes, J. B. (1954) *Brit. med. J.* **1**, 1182.
Schmid, R., Schwartz, S., and Watson, C. J. (1954) *A.M.A. Arch. intern. Med.* **93**, 167.
Scott, J. J. (1955) *Porphyrin Biosynthesis and Metabolism. Ciba Found. Symp.* p. 43. London.
Simici, D. (1938) *Bull. Soc. méd. Hôp. Bucarest*, **9–10**, 321.
Snapper, I. (1922) *Dtsch. med. Wschr.* **48**, 619.
Sowden, G. S. (1910) *Brit. med. J.* **2**, 140.
Spillane, J. D. (1947) *Nutritional Disorders of the Nervous System*, p. 109. Edinburgh.
Stern, R. (1894) *Dtsch. med. Wschr.* Nr. 10, 221.
Stokvis, B. J. (1889) *Ned. T. Geneesk.* **2**, 409.
—— (1895) *Z. klin. Med.* **28**, 1.
Supniewski, J. V. (1927) *J. Physiol.* (*Lond.*) **64**, 30.
Turner, W. J. (1938) *Arch. intern. Med.* **61**, 762.
Urquhart (1898) In discussion, *J. ment. Sci.* **44**, 313.
Vahlquist, B. (1939) *Hoppe-Seylers Z. physiol. Chem.* **259**, 213.
Vannotti, A. (1954) *Porphyrins. Their Biological and Chemical Importance*, trans. C. Rimington. London.
Veflingstad, H. (1949) *Nord. Med.* **42**, 1432.
Waldenström, J. (1937) *Acta med. scand.* Suppl. **82**.
—— (1939) *Acta psychiat.* (*Kbh.*) **14**, 375.
—— (1940) *Svenska Läk.-Tidn.* **37**, 1537.
—— (1944) *Nord. Med.* **23**, 1562.
—— (1956) *Acta genet.* (*Basel*) **6**, 122.
Watson, C. J. (1954) *Advanc. intern. Med.* **6**.
—— and Schwartz, S. (1941) *Proc. Soc. exp. Biol.* (*N.Y.*) **47**, 393.
Wehrmacher, W. H. (1952) *A.M.A. Arch. intern. Med.* **89**, 111.
Westall, R. G. (1952) *Nature* (*Lond.*) **170**, 614.
Whittaker, S. R. F., and Whitehead, T. P. (1956) *Lancet*, **1**, 547.
With, T. K. (1957) *J. clin. Path.* **10**, 165.

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STATISTICAL METHODS APPLIED TO THE CLINICAL DIAGNOSIS OF THYROTOXICOSIS[1]

By J. CROOKS, I. P. C. MURRAY, and E. J. WAYNE

(From the University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow)

Most physicians would agree that, while the diagnosis of thyrotoxicosis is often easy, there are many cases which give rise to uncertainty. This is especially so when the clinical picture is incomplete, or when atypical features are present, and in these circumstances even experienced clinicians may differ in their conclusions. Sometimes the same observer may alter his opinion on the same case on consecutive days. The reason for this state of affairs is not immediately obvious, but it seems to depend on the nature of the mental processes involved in arriving at a diagnosis. In making his clinical assessment a physician must first obtain a reliable history and elicit accurately the appropriate physical signs. At this stage we encounter 'observer variation', since there is rarely complete agreement even among a group of experienced clinicians. Next, the physician must decide upon the relative importance he should attach to the diagnostically significant clinical features of the case. In so doing he falls back on his own experience or, if he is junior, on that of his teachers. At this point further differences of opinion arise, partly owing to the different degree of significance attached to certain features by different clinicians, and partly because of the influence of a fortuitous run of positive or negative findings occurring towards the end of the clinical examination. It is because of these difficulties in making a diagnosis on clinical grounds alone that so many tests of thyroid function have been devised and are so widely used. This in its turn has had the unfortunate effect of making some clinicians feel that they must always have laboratory confirmation of their diagnoses even in the most obvious cases, or, what is worse, of making them place too much significance on laboratory results which run counter to their clinical judgement. As Bauer (1956) has said, 'for these physicians the clinical evaluation lacks that one tangible asset, a figure reported in per cent. elevation, per cent. uptake or gamma per cent.'

Few comparisons have so far been reported between the initial diagnosis made by a clinician at his first interview with the patient and the results of laboratory tests. The present study was initially devised to make this comparison, but, by adopting a statistical procedure incorporating some of the principles of discriminant analysis (Rao, 1948; Zieve and Hill, 1955 *a*), it was found possible to increase the accuracy of the initial clinical diagnosis and to study the effects

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of 'observer variation'. The method consisted in allocating a positive or negative score to each clinical feature, the values being based on an analysis of the relative frequency of symptoms and signs in the disease. In this way a total score, or clinical diagnostic index, can be obtained in each case. We shall produce evidence that there is a wide difference between these scores in frankly thyrotoxic patients and in normal persons, and we believe that in practice the index is helpful in distinguishing between toxic and non-toxic patients in cases presenting diagnostic difficulty. It also provides a numerical estimate of the degree of severity of the disease, which can be correlated with other indices of thyroid function.

The Development of the Clinical Diagnostic Index in Thyrotoxicosis

I. Study of definitely non-toxic and toxic subjects

Subjects examined. The group studied consisted of 182 cases, of which 99 were unquestionably non-toxic and 83 unquestionably thyrotoxic. The non-toxic section of this group included not only normal subjects, mainly medical and nursing staff, but also patients with simple goitres, anxiety states, and post-menopausal symptoms. This group is termed 'definite' in the tables and discussion.

TABLE I

Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis

Symptoms of recent onset or increased severity	*Present (score)*	*Absent (score)*	*Signs*	*Present (score)*	*Absent (score)*
Dyspnoea on effort	+1		Palpable thyroid	+3	−3
Palpitations	+2		Bruit over thyroid	+2*	−2
Tiredness	+2		Exophthalmos	+2	
Preference for heat (irrespective of duration)		−5	Lid retraction	+2	
Preference for cold	+5		Lid lag	+1	
Indifferent to temperature	0		Hyperkinetic movements	+4	−2
Excessive sweating	+3		Fine finger tremor	+1	
Nervousness	+2		Hands:		
Appetite increased	+3		Hot	+2	−2
Appetite decreased		−3	Moist	+1	−1
Weight increased		−3	Casual pulse rate:		
Weight decreased	+3		Auricular fibrillation	+4	
			Regular rate:		
			Under 80		−3
			80–90	0	
			Over 90	+3	

Method of clinical examination. In each subject the presence or absence of the clinical features, shown in Table I, was recorded. These signs and symptoms were chosen because they had previously been shown by a clinical survey to differ in their incidence in thyrotoxic and normal subjects (Wayne, 1954). We did not use a written questionnaire to elicit symptoms, and the method of history-taking is described in the Appendix. In order to reduce the effects of 'observer variation', the procedure for the physical examination was rigid, and the Appendix describes the criteria to be fulfilled.

The clinical index. The clinical features recorded in the cases which had given rise to no clinical diagnostic difficulty were weighted by allocating a score to each (Table I). The positive or negative values of these scores were initially allocated on the basis of the relative diagnostic significance of each symptom and sign, as found by Wayne (1954) or, in a few instances, by Williams (1950).

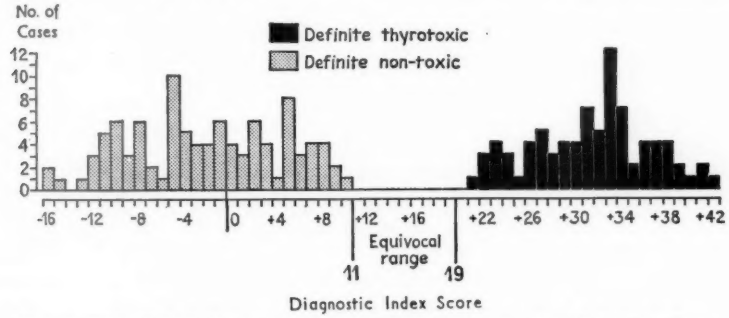

FIG. 1. The clinical diagnostic index applied to cases in the 'definite' group.

These scores were then modified so as to diminish the effects of 'observer variation'. This was done by reducing in value the highest scores because, although attached to features of great diagnostic importance, differences between observers were found to give rise to considerable variation in the total score. The clinical diagnostic indices, or total scores, were then calculated. These scores produced a good separation between non-toxic and toxic subjects; but the weighting factors for the individual clinical features were further modified to produce the widest possible separation between the two groups without reintroducing excessive 'observer variation' effects. The indices were then recalculated.

When the clinical diagnostic indices of the 99 non-toxic and 83 toxic subjects of the definite group were analysed (Table II), the range of values was found to be from −16 to +10 for the former and from +21 to +42 for the latter. Fig. 1 illustrates the distribution of these unequivocally non-toxic and toxic subjects, and the division between them. Thus an index of +10 or under indicated non-toxicity, and indices of +20 or over indicated toxicity. Statistical analysis of the results allowed the probabilities corresponding to the observed percentages, given in Table II, to be calculated:

Clinical diagnostic index	*Definite non-toxic*	*Definite toxic*
+10 and less	0·9738	0·0002
+20 and over	0·0005	0·9893

It will be seen that, for values of the index below +11 and above +19, there is good agreement between the observed percentages of Table II and the above probabilities multiplied by 100. The agreement is due to the fact that 'normal' distributions can be satisfactorily fitted to the definite non-toxic and toxic groups.

II. Study of subjects presenting clinical diagnostic difficulty

Subjects examined and methods. This group, which is subsequently called

'doubtful', consisted of 118 cases, each of which had presented some diagnostic difficulty to one or more hospital physicians. All had been referred for radioiodine studies, and the final diagnosis was made only after prolonged observation, including the response to treatment. We are, however, confident of our final conclusions. At the patients' first visit the presence or absence of the symptoms and signs listed in Table I was recorded by using the criteria described in the Appendix. Clinical indices were calculated only when the final diagnosis was agreed after full investigation and the results of therapy were known.

TABLE II

Comparison of the Clinical Diagnostic Index with Radioiodine Studies and Basal Metabolic Rate Estimations

		'Definite' group		*'Doubtful' group*	
Diagnostic procedures	*Ranges*	*Final diagnosis non-toxic*	*Final diagnosis toxic*	*Final diagnosis non-toxic*	*Final diagnosis toxic*
Clinical diagnostic index	$< +11$	99 (100%)	0	59 (88·1%)	0
	$+11$ to $+19$	0	0	7 (10·4%)	6 (11·8%)
	$> +19$	0	83 (100%)	1 (1·5%)	45 (88·2%)
Total cases		99	83	67	51
4-hour uptake of ^{131}I	$< 46\%$	34 (87·3%)	1 (1·9%)	56 (89·0%)	3 (6·4%)
	$> 45\%$	5 (12·7%)	52 (98·1%)	7 (11·0%)	44 (93·6%)
Total cases		39	53	63	47
48-hour plasma protein-bound ^{131}I	$< 0·4\%$	36 (94·7%)	1 (1·9%)	59 (93·7%)	5 (10·6%)
	$> 0·39\%$	2 (5·3%)	52 (98·1%)	4 (6·3%)	42 (89·4%)
Total cases		38	53	63	47
Basal metabolic rate (Robertson and Reid, 1952)	$< +16\%$	40 (97·6%)	2 (2·9%)	34 (87·4%)	11 (26·9%)
	$> +15\%$	1 (2·4%)	65 (97·1%)	5 (12·6%)	30 (73·1%)
Total cases		41	67	39	41

The clinical diagnostic index. Since the weighting factors allocated to the clinical features in the 'definite' group had produced indices giving a wide separation between toxic and non-toxic cases, the same weightings were adopted in the analysis of the 'doubtful' group. The distribution of the indices in the 118 subjects of this group is shown in Fig. 2. Thirteen subjects had indices lying between $+11$ and $+19$. We have called this the equivocal range. One non-toxic subject had an index lying within the toxic range. A good division persisted, however, between cases finally shown to be non-toxic and those shown to be toxic, 88 per cent. of each lying within the non-toxic and the toxic ranges respectively (Table II). The distribution curves for this group are shown in Fig. 3. Statistical analysis of the results allowed the probabilities corresponding to the observed percentages, given in Table II, to be calculated:

Clinical diagnostic index	*Doubtful non-toxic*	*Doubtful toxic*
$+10$ and less	0·8315	0·0035
$+20$ and over	0·0107	0·8051

For values of the index below $+11$ there was reasonably good agreement in the non-toxic group between the above probability multiplied by 100 and the

observed percentage in Table II. As in the case of the 'definite' group, this was due to the fact that a 'normal' distribution could be fitted to the 'doubtful' non-toxic subjects. In the case of the 'doubtful' toxic group, however, a 'normal' distribution did not provide a good fit to the observed distribution, and this may be partly or wholly due to the relatively small number (51) of patients in this group.

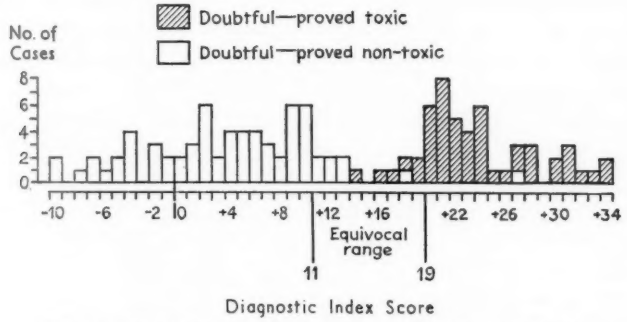

FIG. 2. The clinical diagnostic index applied to cases in the 'doubtful' group.

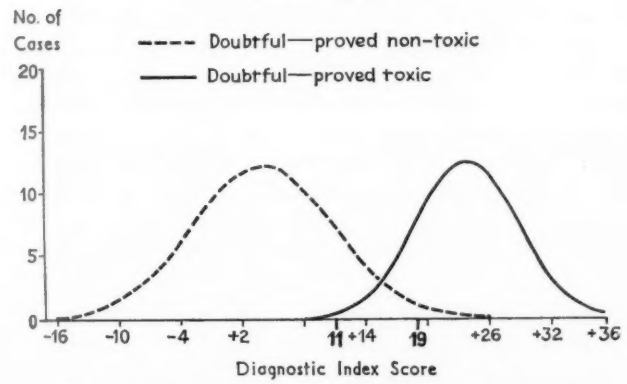

FIG. 3. Distribution curves of clinical diagnostic indices of cases in the 'doubtful' group.

'Observer variation' studies. Nine patients, not included in the present series, whose thyroid function was difficult to assess clinically, were chosen. Nine observers carried out an independent assessment of these patients, using the scoring sheet shown in Table I. This group consisted of the authors, two consultant physicians, one research fellow, one senior house officer, one house physician, and one medical student in his final year. The medical student was given special training in our criteria and careful instructions as to the use of the scoring sheet. The observers were thus chosen to include a wide variation of experience both in general medicine and in thyroid disorders. The results are shown in Table III. Analysis of variance of the indices in 63 observations carried out by Observers 1 to 7 showed no significant difference ($f = 1{\cdot}62$). Observers 8

(the research fellow) and 9 (the senior house officer), both of whom were newcomers to the unit, scored systematically lower.

A further nine patients were similarly assessed by one of the authors, and by a newcomer to the department with a wide experience of thyroid disease gained at another centre. This physician was given only typewritten instructions as to the use of the scoring sheet. The results are shown at the foot of Table III. There was no significant difference in analysis of variance of their scores ($f = 2{\cdot}06$).

TABLE III

Results of 'Observer Variation' Studies using the Clinical Diagnostic Index

	Case									Mean values
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	
Observer 1	+24	−3	+14	+13	0	+10	+35	+35	+31	18·7
2	+29	+2	+15	+18	−1	+7	+37	+25	+21	17·0
3	+31	+1	+5	+19	−4	+1	+39	+34	+22	16·4
4	+20	+1	+4	+12	−8	+3	+39	+26	+25	13·6
5	+21	−7	+7	+14	−6	+10	+33	+26	+30	14·2
6	+30	−2	+17	+16	−2	0	+33	+32	+24	16·4
7	+29	−3	+15	+6	−5	−3	+36	+24	+26	13·9
8	+25	−7	+11	0	−2	−1	+25	+25	+29	11·7
9	+22	−11	+11	−1	−5	−5	+30	+26	+23	10·0
	J	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*R*	*Mean*
Observer 3	−4	+22	+2	+31	+25	+17	+22	+32	+17	18·2
10	−1	+16	−5	+34	+22	+12	+22	+34	+13	16·3

III. Comparison of the clinical diagnostic index with laboratory tests

Radioiodine studies. Full studies were carried out in 91 of the cases presenting no clinical diagnostic difficulty ('definite' group) and in 110 of those in which initial diagnostic difficulty had been found ('doubtful' group). These studies consisted of the estimation of the gland uptake of radioiodine and the protein-bound plasma radioactivity, four and 48 hours respectively after the administration of 25 μc of ^{131}I. The techniques used have been previously described by Ansell, Macgregor, Miller, and Wayne (1953). The method of estimating protein-bound ^{131}I has, however, been simplified by the use of an ion-exchange resin.

The results of measurements of the four-hour uptake of radioiodine in 202 subjects are shown in Table II. In this department the upper limit of the normal range of the four-hour uptake of radioiodine is taken as 45 per cent. of the dose. In 87 per cent. of the non-toxic cases included in the 'definite' group, in which the diagnosis was never in doubt, the uptake was within our normal limits. It was greater than this value in 98 per cent. of the toxic cases of this group. In the 'doubtful' group the diagnostic accuracy of the uptake was of the same order as that of the clinical index for the same group: 89 per cent. of non-toxic cases (88 per cent. by the index) and 94 per cent. of toxic cases (88 per cent. by the index) were correctly diagnosed by this test.

Estimations of the protein-bound radioactivity of the plasma at 48 hours

were made in 201 subjects (Table II). In non-toxic cases 95 per cent. of the 'definite' group and 94 per cent. of the 'doubtful' group had values of less than 0·4 per cent. of the dose per litre of plasma, which is considered by us to be the lower limit of the range indicating hyperthyroidism. In toxic cases the protein-bound ^{131}I was above this level in 98 per cent. of the 'definite' group and 89 per cent. of the group which had given diagnostic difficulty. Statistical analysis shows no significant difference between the index and the radioiodine studies in the proportion of correct diagnoses achieved.

The basal metabolic rate was estimated in 108 subjects of the 'definite' group and in 80 subjects of the 'doubtful' group. All the estimations were carried out by one experienced technician using a Benedict–Roth apparatus. Patients were admitted to hospital, and were given 200 mg. of butobarbitone 12 hours before each test. The tests were carried out in duplicate on two successive days, and the lowest of four estimations accepted, the standards of Robertson and Reid (1952) being used. Further details of the method are given by Crooks, Murray, and Wayne (1958). The results of the 188 basal metabolic rate estimations are shown in Table II. In 98 per cent. of the non-toxic subjects of the 'definite' group the basal metabolic rates were within the normal range of the Robertson and Reid standards. The basal metabolic rate was raised in 97 per cent. of toxic subjects of this group. Basal metabolic rates within the normal range were found in 87 per cent. of the cases presenting diagnostic difficulty and finally shown to be non-toxic, while only 73 per cent. of the toxic subjects of this group had elevated values. Statistical analysis shows no difference between the index and estimations of the basal metabolic rate as regards the proportion of correct diagnoses achieved.

Application of the Clinical Diagnostic Index

I. An aid to diagnosis in routine clinical practice

In order to obtain information on the diagnostic accuracy of the method in the hands of independent observers, score sheets, with written instructions for their use, were sent to three other hospitals (Table IV, Hospitals B, C, and D) in Scotland. At their routine clinics a total of 121 patients referred for assessment of thyroid function were selected at random, and score sheets completed. The final diagnosis, usually based on a conventional clinical assessment, radioiodine studies, and basal metabolic rate estimations, was confirmed by therapeutic trial or observation. It can be seen from Table IV that the diagnostic accuracy obtained in this group of subjects was of the same order as that found in the doubtful group of the original series. The practical application of the index was also assessed by us on a further 50 patients referred to the clinic by other physicians because diagnostic difficulty had been found. In the case of these subjects indices were obtained before any further clinical assessment was made or laboratory investigation carried out. The final diagnosis was reached after full investigation and follow-up, including therapeutic trials in some cases. The index gave the correct diagnosis in 43 (86 per cent.) of the 50 cases (Table IV,

Hospital A). Of the remaining seven cases, in all of which the index lay within the equivocal range, three were finally shown to be toxic and four non-toxic. The total number of correct diagnoses, 149 of 171 subjects (85 per cent.) in this additional investigation is comparable with the results obtained by the application of our method to the 'doubtful' group of the original series. It is most important to note that, of the 22 cases which were not correctly placed in toxic or non-toxic categories, the diagnosis was completely misleading in only five subjects (3 per cent.), since 17 fell within the equivocal range, thus indicating a suspension of judgement until further tests had been carried out.

TABLE IV

Results of the Clinical Diagnostic Index in Different Hospitals

Hospital	*Number of cases*	*Agreement with final diagnosis*
A	50	86%
B	74	84%
C	24	88%
D	23	83%
Total	171	85%

II. The use of the index in selected cases to illustrate the technique of clinical diagnosis

We believe that a conventional clinical diagnosis involves the unconscious application of the principles underlying discriminant analysis (Rao, 1948; Zieve and Hill, 1955*a*), and we have selected examples of the use of the clinical diagnostic index, from both the 'definite' and the 'doubtful' groups of the original series, to illustrate some of the sources of diagnostic difficulty.

1. The toxic members of the *'definite' group* are of lesser interest, and the correct diagnosis would have been made with ease by conventional clinical methods. It is, however, worth while to look more closely at three groups of non-toxic subjects, in each of which an inexperienced observer might have been confused by the presence of several symptoms usually associated with the thyrotoxic state.

Post-menopausal subjects. It has been suggested by Wayne (1954) that post-menopausal women show many of the symptoms of thyrotoxicosis, for example dyspnoea, tiredness, and excessive sweating, and that because of this such cases may cause diagnostic difficulty. He considered, however, that an experienced physician, because of his skill in history-taking, would be unlikely to misinterpret this clinical picture. When the index was applied to such patients they gained, as was expected, high symptom scores, but these were nullified by their negative sign scores because of the absence of physical signs of high diagnostic significance. This is well shown in the following post-menopausal subject:

A woman aged 51 years (last menstrual period 16 months previously)

Symptoms

Dyspnoea on effort	(+1)	Preference for cold	(+5)
Palpitations	(+2)	Increased weight	(−3)
Tiredness	(+2)		

Symptom score = +7

Signs

Goitre absent	(−3)	Hands cool	(−2)
Bruit absent	(−2)	Hands dry	(−1)
Hyperkinesis absent	(−2)	Casual pulse rate 84 per minute	(0)

Sign score = −10

Diagnostic index: −3.

Radioiodine studies: four-hour uptake 50 per cent., 48-hour protein-bound radioactive iodine 0·12 per cent. per litre.

Basal metabolic rate: +14 per cent.

Final diagnosis: Non-toxic, confirmed by observation.

It can be seen that, in spite of the negative score for increase of weight, the patient still scored +7 on symptoms. The negative values allocated to absent physical signs, however, more than compensated for this score.

Normal young women with some features of thyrotoxicosis. These subjects were found among a group of nurses, fully employed, who made no spontaneous complaints. An example of this type of subject is shown below:

A woman aged 19 years

Symptoms

Dyspnoea on effort	(+1)	Increased appetite	(+3)
Tiredness	(+2)	Increased weight	(−3)
Excessive sweating	(+3)		

Symptom score = +6

Signs

Goitre absent	(−3)	Fine finger tremor	(+1)
Bruit absent	(−2)	Hands hot	(+2)
Exophthalmos	(+2)	Hands moist	(+1)
Hyperkinesis absent	(−2)	Casual pulse rate 86 per minute	(0)

Sign score = −1

Diagnostic index: +5.

The relatively high symptom score in this subject is not supplemented by a raised sign score and, although she had several of the signs found in thyrotoxicosis, these were the least heavily weighted. She expressed, for example, a preference for cold weather and admitted to nervousness, but these symptoms had been present for as long as she could remember, and for this reason lost their diagnostic importance.

Anxiety states. This group of cases may cause diagnostic difficulty to the inexperienced clinician, and accounts for a large proportion of the patients referred for radioiodine studies in whom the tests prove negative. This is especially the case if a goitre is also present. The absence of diagnostically

important physical signs, however, compensates for the high symptom scores, as in the following example:

A woman aged 33 years

Symptoms

Dyspnoea on effort	(+1)	Preference for cold	(+5)
Palpitations	(+2)	Excessive sweating	(+3)
Tiredness	(+2)	Nervousness	(+2)

Symptom score = +15

Signs

Goitre absent	(−3)	Fine finger tremor	(+1)
Bruit absent	(−2)	Hands cool	(−2)
Hyperkinesis absent	(−2)	Hands moist	(+1)
		Casual pulse rate 88 per minute	(0)

Sign score = −7

Diagnostic index: +8.

Radioiodine studies: four-hour uptake 36 per cent., 48-hour protein-bound radioactive iodine 0.

Basal metabolic rate: +13 per cent.

Final diagnosis: Non-toxic, confirmed by observation.

2. *Subjects presenting initial diagnostic difficulty* (*the 'doubtful' group*) are of greater interest, since they include the type of case which affords difficulty even to the experienced clinician. In order to find out why this difficulty arose, an analysis was made of this group, and the cases appeared to fall into the following categories:

Toxic cases with many symptoms, but few signs. It is probable that these patients were referred to us chiefly because the positive signs appeared to be too few to allow a definite diagnosis to be made. The following patient complained of nearly all the more important symptoms of thyrotoxicosis, but few signs were present. The index, however, gave a correct diagnosis.

A woman aged 55 years

Symptoms

Dyspnoea on effort	(+1)	Excessive sweating	(+3)
Palpitations	(+2)	Nervousness	(+2)
Tiredness	(+2)	Decreased weight	(+3)
Preference for cold	(+5)		

Symptom score = +18

Signs

Goitre	(+3)	Fine finger tremor	(+1)
Bruit absent	(−2)	Hands hot	(+2)
Lid retraction	(+2)	Hands moist	(+1)
Hyperkinesis absent	(−2)	Casual pulse rate 70 per minute	(−3)

Sign score = +2

Diagnostic index: +20.

Radioiodine studies: four-hour uptake 69 per cent, 48-hour protein-bound radioactive iodine 0·3 per cent. per litre.

Basal metabolic rate: +14 per cent.

Final diagnosis: Toxic, confirmed by response to methyl-thiouracil therapy.

Toxic cases with few or atypical symptoms and many signs. Most physicians tend to regard positive physical signs as more reliable than positive symptoms, and this group rarely gives rise to diagnostic difficulty unless the patient has symptoms which are regarded as highly unusual in a toxic patient. The following case, for example, is an exception to the rule that thyrotoxic patients are intolerant of heat. The numerous positive signs more than compensated for this atypical feature, and the index gave the correct diagnosis:

A man aged 67 years

Symptoms

Preference for heat	(−5)	Loss of weight	(+3)
Nervousness	(+2)		

Symptom score = 0

Signs

Goitre	(+3)	Hyperkinesis	(+4)
Bruit present	(+2)	Fine finger tremor	(+1)
Exophthalmos	(+2)	Hands hot	(+2)
Lid retraction	(+2)	Hands moist	(+1)
Lid lag	(+1)	Casual pulse rate 100 per minute	(+3)

Sign score = +21

Diagnostic index: +21.

Radioiodine studies: four-hour uptake 83 per cent., 48-hour protein-bound radioactive iodine 4·25 per cent. per litre.

Basal metabolic rate: +76 per cent.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy.

Toxic cases with highly significant features missing. In these cases, despite a fairly complete clinical picture, there had been a reluctance to arrive at a definite clinical diagnosis because of the absence of one or more features classically found in hyperthyroidism. In the following case there was no goitre:

A man aged 63 years

Symptoms

Dyspnoea on effort	(+1)	Excessive sweating	(+3)
Palpitations	(+2)	Decrease of weight	(+3)
Preference for cold	(+5)		

Symptom score = +14

Signs

Goitre absent	(−3)	Hyperkinesis	(+4)
Bruit absent	(−2)	Fine finger tremor	(+1)
Exophthalmos	(+2)	Hands hot	(+2)
Lid retraction	(+2)	Hands dry	(−1)
Lid lag	(+1)	Auricular fibrillation	(+4)

Sign score = +10

Diagnostic index: +24.

Radioiodine studies: four-hour uptake 68 per cent., 48-hour protein-bound radioactive iodine 1·1 per cent. per litre.

Basal metabolic rate: +11 per cent.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy.

It should be noted that this was a male patient, and it is recognized that hyperthyroidism without a goitre may not infrequently occur in men. Indeed, it was suggested that the diagnostic accuracy of the index might be improved by omitting the negative score where the gland was not palpable in a male subject, but it was decided that this would increase the complexity of the scoring system. The incidence of the disease in male subjects is in any case low, and they represent 18 per cent. of the present series and 21 per cent. of a larger series reviewed by Skanse (1949).

TABLE V

Subjects with Indices lying in the Equivocal Range, and One Non-thyrotoxic Subject with an Index in the Toxic Range

				Clinical diagnostic Index			*Radioiodine studies*		
Subject number	*Sex*	*Age (years)*	*Final diagnosis*	*Symptom score*	*Sign score*	*Total score*	*4-hr. gland uptake (% dose)*	*Plasma protein-bound activity at 48 hrs. (% dose/litre)*	*Basal metabolic rate (%)*
1	F	52	Non-toxic	+9	+2	+11	29·0	0·09	+8
2	F	20	Non-toxic	+12	−1	+11	62·4	0·0	+3
3	F	49	Non-toxic	+10	+2	+12	45·0	0·09	+9
4	F	37	Non-toxic	+7	+5	+12	35·0	0·0	0
5	F	46	Non-toxic	+7	+6	+13	40·0	0·0	+3
6	F	72	Non-toxic	+12	+1	+13	17·3	0·0	−4
7	F	45	Toxic	+2	+12	+14	84·9	0·63	+65
8	F	52	Toxic	+5	+11	+16	65·8	0·68	+4
9	F	51	Toxic	+7	+10	+17	50·5	0·44	+29
10	F	36	Non-toxic	+13	+5	+18	18·5	0·0	+7
11	F	47	Toxic	+16	+2	+18	62·3	0·29	+20
12	F	34	Toxic	+9	+10	+19	71·0	1·05	+28
13	M	50	Toxic	+14	+5	+19	65·0	0·90	+20
14	F	34	Non-toxic	+16	+11	+27	41·7	0·17	+6

Thyrocardiac subjects (*'masked' hyperthyroidism*). Thyrotoxicosis in patients with auricular fibrillation, with or without cardiac failure, who do not show the classical features of thyrotoxicosis, is notoriously liable to elude diagnosis. Thus Bortin, Silver, and Yohalem (1951) investigated 55 cases of auricular fibrillation in which the aetiology was not obvious, and decided on the results of radioiodine studies that eight were examples of 'masked' hyperthyroidism. In our series of cases all of 13 patients with thyrotoxic auricular fibrillation were correctly placed by the index, although we have since seen one patient who fell within the equivocal range. The index should be used with caution in patients with congestive cardiac failure, since they usually score points (+6 or +7) for dyspnoea, palpitations, and either tachycardia or auricular fibrillation, even if they are not thyrotoxic. Radioiodine studies or estimations of protein-bound iodine are of great diagnostic help in such cases.

Subjects with several atypical features, and with indices in the equivocal range. The findings in 13 cases with diagnostic indices lying in the equivocal range, and

in one non-toxic case with an index in the toxic range, are worth special consideration. Some details are given in Table V. Within this group the non-toxic cases appear to lie at the lower limits, and the toxic cases at the upper limits, of the equivocal range. From the distribution curves of the non-toxic and toxic cases of the 'doubtful' group, however, it can be calculated that if a subject has a score which falls within the equivocal range the possibilities of toxicity or non-toxicity are equal (Fig. 3). The reason why a toxic case may fall within this equivocal range is almost always the absence of features of high diagnostic significance, as illustrated by the following case:

Case 9. A woman aged 51 years

Symptoms

Dyspnoea on effort	(+1)	Nervousness	(+2)
Palpitations	(+2)	Increase of weight	(−3)
Preference for cold	(+5)		

Symptom score = +7

Signs

Goitre	(+3)	Hands hot	(+2)
Bruit absent	(−2)	Hands dry	(−1)
Hyperkinesis	(+4)	Casual pulse rate 105 per minute	(+3)
Fine finger tremor	(+1)		

Sign score = +10

Diagnostic index: +17.

Radioiodine studies: four-hour uptake 50 per cent., 48-hour protein-bound radioactive iodine 0·44 per cent. per litre.

Basal metabolic rate: +29 per cent.

Final diagnosis: toxic, confirmed by response to methyl thiouracil therapy. Conventional diagnostic methods would possibly have placed this patient correctly.

Non-toxic subjects falling within the equivocal range were usually patients with severe anxiety states. They had high symptom scores associated with one or two heavily weighted signs, for example the presence of goitre or tachycardia. Negative scores arising from the physical examination did not compensate for positive symptom scores, as illustrated in the following case:

Case 3. A woman aged 49 years

Symptoms

Dyspnoea on effort	(+1)	Excessive sweating	(+3)
Tiredness	(+2)	Nervousness	(+2)
Preference for cold	(+5)	Decrease of appetite	(−3)

Symptom score = +10

Signs

Goitre	(+3)	Fine finger tremor	(+1)
Bruit absent	(−2)	Hands hot	(+2)
Lid lag	(+1)	Hands dry	(−1)
Hyperkinesis absent	(−2)	Casual pulse rate 90 per minute	(0)

Sign score = +2

Diagnostic index: +12.

Radioiodine studies: four-hour uptake 45 per cent., 48-hour protein-bound radioactive iodine 0·09 per cent. per litre.

Basal metabolic rate: +9 per cent.

Final diagnosis: Non-toxic, confirmed by failure to respond to methyl-thiouracil therapy.

Only two cases of this group, Nos. 2 and 11, were not correctly diagnosed by radioiodine tests. The basal metabolic rate estimations were diagnostically correct in all but one subject of this group (No. 8).

Non-toxic cases after thyroidectomy, with indices in the toxic range. This group includes cases which are apt to be wrongly assessed both by the index and by conventional clinical methods. The patients, who at some time in the past have suffered from thyrotoxicosis, are well aware of the symptoms of the disorder. If in addition they have tachycardia, goitre, or eye signs, they tend to score heavily. Unfortunately radioiodine studies often give misleading results in this group, and the most reliable objective evidence is afforded by estimations of the basal metabolic rate or of protein-bound iodine. A therapeutic trial using an antithyroid drug is often the most effective way of arriving at a correct conclusion. The following case is an example:

Case 14. A woman aged 34 years

Symptoms

Dyspnoea on effort	(+1)	Preference for cold	(+5)
Palpitations	(+2)	Appetite increased	(+3)
Tiredness	(+2)	Weight decreased	(+3)

Symptom score = +16

Signs

Goitre	(+3)	Fine finger tremor	(+1)
Bruit present	(+2)	Hands hot	(+2)
Exophthalmos	(+2)	Hands dry	(−1)
Lid lag	(+1)	Casual pulse rate 76 per minute	(−3)
Hyperkinesis	(+4)		

Sign score = +11

Diagnostic index: +27.

Radioiodine studies: four-hour uptake 42 per cent., 48-hour protein-bound radioactive iodine 0·17 per cent. per litre.

Basal metabolic rate: +6 per cent.

Final diagnosis: Non-toxic, confirmed by failure to respond to methyl thiouracil therapy.

III. The index as a measure of severity

In thyrotoxic patients the index gives a quantitative measure of the severity

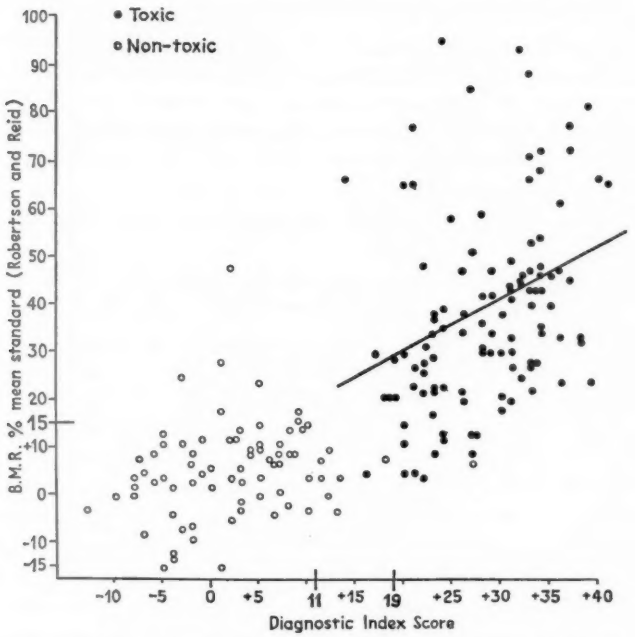

FIG. 4. The clinical diagnostic index used as a measure of severity and correlated with the basal metabolic rate. The regression line of the index on the basal metabolic rate in toxic cases is shown.

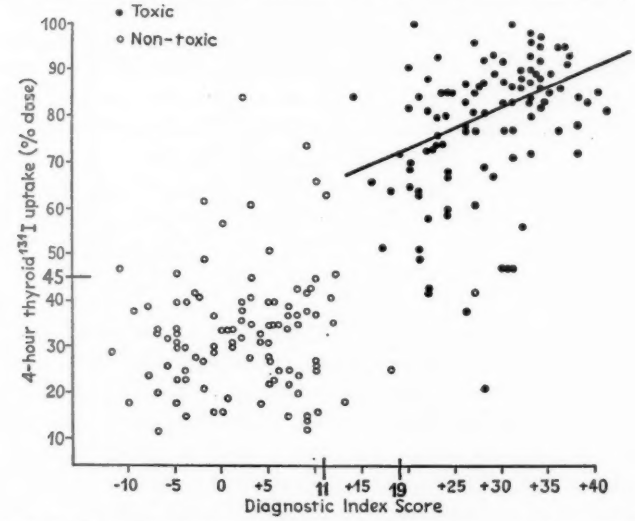

FIG. 5. The clinical diagnostic index used as a measure of severity and correlated with the four-hour gland uptake of radioiodine. The regression line of the index on the four-hour gland uptake of radioiodine in toxic cases is shown.

of the disease as judged by the presence of symptoms and signs. It is of interest, therefore, to see the extent to which it correlates with laboratory findings. When the values for basal metabolic rate estimations were plotted against the indices in 188 cases, a significant correlation ($r = 0{\cdot}33$) was present in thyrotoxic subjects (Fig. 4). The values for the four-hour uptake of radioiodine were

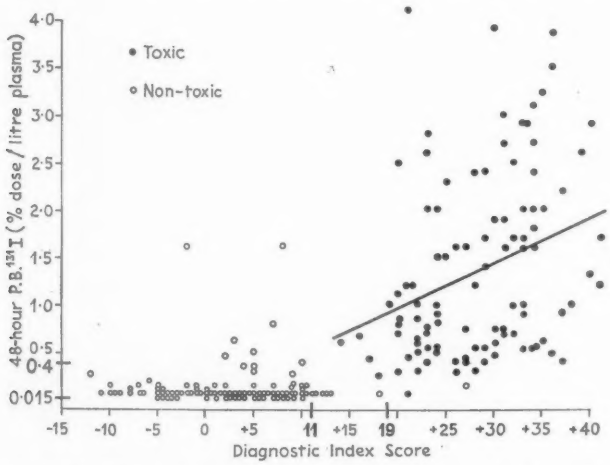

FIG. 6. The clinical diagnostic index used as a measure of severity and correlated with the 48-hour plasma protein-bound radioactivity. The regression line of the index on the 48-hour plasma protein-bound radioactivity is shown.

plotted against the indices in 202 cases (Fig. 5), and a significant correlation was found in the thyrotoxic subjects ($r = 0{\cdot}36$). A similar degree of correlation ($r = 0{\cdot}36$) was found in thyrotoxic subjects between the index and the values for 48-hour protein-bound plasma radioactivity (Fig. 6).

Discussion

The process of making a clinical diagnosis is complicated. It involves the sifting and evaluating of multiple symptoms and signs, and results in the selection of the clinical syndrome which accounts best for the findings. The clinician attaches greater or lesser significance to the clinical features, according to his past experience. He combines the findings into a formula, often subconsciously, by applying the concepts of multiple correlation in a non-quantitative manner, and in this way arrives at a diagnosis (Zieve and Hill, 1955*a*). The clinical diagnostic index applies this principle at a conscious level. Previously this method has been used mainly in the evaluation of laboratory investigations. For example, Zieve and Hill (1955*b*), after studying 11 liver function tests, found that four

could be combined to produce a 'cirrhosis abnormality score' which discriminated well between normal and cirrhotic subjects. Oyama and Tatsuoka (1956) used a similar technique to assess the prognosis of patients with pulmonary tuberculosis. Using 13 characteristics, they constructed an equation from which a score could be calculated for each patient. This score discriminated with 75 per cent. accuracy between those who eventually relapsed and those who remained well. In the field of thyroid disease Schultz and Zieve (1956) have attempted with some success to predict a remission of thyrotoxicosis, after a single dose of radioactive iodine, from a score obtained by allocating weighted values at intervals after therapy to the clinical state, the thyroid uptake of ^{131}I, the basal metabolic rate, and the level of serum cholesterol.

In order to apply the technique to clinical diagnosis, it is necessary first to carry out a symptom analysis in patients suffering from a particular disease and in control subjects. The diagnostic significance of each feature can then be determined. A symptom analysis of thyrotoxicosis carried out by one of us (Wayne, 1954) provided this necessary information, and was used in the provisional allocation of diagnostic values to the various symptoms and signs. In this analysis it was apparent that the features most helpful in reaching a diagnosis were increased appetite, loss of weight, preference for cold weather, hot sweating hands, persistent tachycardia, and hyperkinesis. It can be seen from Table I that these are the features which have been given the highest positive scores. Additional features, such as a bruit over the gland and excessive sweating, have also been weighted heavily, since Williams (1950) has shown them also to be of high diagnostic significance. When clinical diagnosis is taught or practised, emphasis tends to be placed on the presence of certain symptoms and signs, but in many instances the absence of these features may be of equal importance. For example, the absence of peripheral vasodilation favours the diagnosis of non-toxicity to the same extent that its presence favours toxicity. In order, therefore, to make the greatest possible use of the clinical evidence, equivalent negative values were allocated to some of the features which carried the highest positive scores. This is illustrated by the weightings given to a palpable gland and bruit over the gland. Thus a goitre (+3) with a bruit (+2) scores +5, while a goitre (+3) without a bruit (−2) scores +1. The values placed on the presence or absence of hyperkinesis, +4 and −2 respectively (originally +5 and −5), are examples of the modifications made in the initial scores in order to minimize the effect of 'observer variation', for it was soon appreciated that hyperkinesis, although in our view of considerable diagnostic significance, may be difficult for those clinicians to recognize to whom we have been unable to demonstrate our criteria. The justification, however, for the retention of its heavy weighting is the frequent presence of the sign in atypical cases which show few other positive features. The decrease in the weighting of other highly significant diagnostic features was designed to make it impossible for a single observation of any one feature, however diagnostically important, to alter a patient's total score so greatly as to move it from the toxic to the non-toxic range, or vice versa.

We were satisfied that in our hands the index was reliable; but the value of diagnostic procedures, clinical, chemical, and physical, depends to a large extent on their reproducibility, and the greater the human element in a method the higher is the probability of variation when the observations are repeated. History-taking is prone to error, as Cochrane, Chapman, and Oldham (1951) have shown, and it is difficult to diminish the effects of 'observer variation', since they arise in the mind of the patient as well as in the interpretation of his statements by the physician. We avoided using a written questionnaire, since Glaser and Whittow (1954) have shown its unreliability. Ninety per cent. of their normal subjects so questioned at first recorded at least one symptom, but when the questionnaire was repeated there was a significantly smaller number of positive responses. Wayne (1954) also noted a high incidence of positive responses in a normal control group in reply to set questions, but suggested that appropriate supplementary questions would reduce this effect. In the present series the history was taken by conventional methods, leading questions were avoided, and appropriate supplementary questions were asked about each symptom. Inconsistencies in the recording of physical signs have been demonstrated by Fletcher (1952) in a study in which eight observers, all Members or Fellows of a College of Physicians, independently elicited the physical signs found in the chest of each of 20 patients suffering from emphysema. With most signs only two-thirds agreement was obtained. He suggested, however, that agreement might be improved by laying down more rigid criteria for the presence or absence of physical signs. The improvement in agreement between observers when the criteria for physical signs can be clearly defined has been demonstrated by Schilling, Hughes, and Dingwall-Fordyce (1955), who compared the accuracy of two observers in making the diagnosis of byssinosis. It was for this reason that rigid definitions of physical signs were laid down in the present series.

The results of the 'observer variation' studies (Table III) show that in the case of Observers 1 to 7 these precautions were successful. It is of interest that Observer 7, the senior medical student, who had had careful and detailed instruction in history-taking and in the criteria for physical signs, showed no statistically significant difference in mean total score from the more experienced observers. Observers 8 and 9, however, who had no special experience of thyroid disease and, having only recently joined the Unit, had received no special instruction, scored systematically lower. It might be objected that the close agreement between the total scores of Observers 1 to 7 reflects their common experience and training. It was to test this objection that Observer 10, whose experience has been gained in another department, was asked to obtain the total scores in nine patients within one week of his arrival in this department. There was no significant difference between his mean total score and that of one of the authors. There was usually some disagreement between observers in the recording of individual symptoms and signs; in eight out of 10 observers this was insufficient to alter significantly their mean total scores. These 'observer variation' studies suggest that no statistically significant difference will be obtained by observers using the diagnostic index, provided they have some experience of thyroid

disease. It is also clear that, with the ranges of normality and abnormality used in the present study, inexperienced observers tend to score low, and may fail to reach a diagnosis in a number of mildly toxic cases. Most of these cases, however, will fall into the equivocal range, thus indicating the need for further investigation.

It is customary, in assessing the accuracy of tests of thyroid function, to correlate them with the final diagnosis arrived at after prolonged observation. Few workers have attempted to correlate the initial clinical diagnosis, based on signs and symptoms alone, with either the results of laboratory investigations or with the final diagnosis. The view is generally accepted that tests involving the use of radioiodine are especially reliable, although different observers favour different techniques. In this department the uptake of the thyroid gland is measured four hours after a dose of radioiodine has been administered, and the protein-bound plasma radioiodine 48 hours after the dose. These tests in the present series have a diagnostic accuracy of the same order as that described by Wayne (1954) and Macgregor and Wayne (1957). They were carried out in nearly all cases of our 'doubtful' group, and we were therefore able to correlate the results with both the initial diagnosis given by the clinical index and with the final diagnosis. Comparison of the radioiodine tests with the clinical index is rendered a little difficult, because radioiodine tests assign patients definitely to either toxic or non-toxic groups, whereas the clinical index may place some patients in an equivocal group. There was, however, no statistically significant difference in accuracy between the index and either of the radioiodine tests, even when the equivocal results given by the index were regarded as entirely incorrect. Estimations of the basal metabolic rate were obtained in 80 patients of the 'doubtful' group, and Table II shows that the rate was within the normal range in about one-quarter of the toxic subjects of this group. Even if all the equivocal indices are counted as incorrect, the basal metabolic rate has no statistically significant advantage in diagnostic accuracy over the index. It should be pointed out that, irrespective of the diagnostic procedure used, our final decision was based on the response to therapy, and it follows that for our present purpose we define thyrotoxicosis as a condition in which antithyroid therapy produces a remission of symptoms and signs. This definition has the great advantage that it supplies the essential information which a physician requires.

We have described the evidence which has convinced us that the clinical index is of practical value. This opinion was confirmed by the results obtained by other hospitals using the method in their routine clinical practice. It is of special importance to note (Table IV) that, of the 121 patients assessed by the index at other hospitals, only 15 were not correctly placed in toxic or non-toxic categories, and 10 of these were placed in the equivocal group, indicating the need for further investigation. In only five cases was the diagnosis completely incorrect. In one of the hospitals a study was made of the results obtained by medical students who had not been specially trained in the use of the scoring sheets, and our findings of the fallacies introduced by inexperience were

confirmed. While the independent observers were satisfied that the method provided good discrimination between toxic and non-toxic subjects, the opinion was expressed by one physician that his overall clinical assessment would have produced a separation of the same order. Further observations would have to be made to confirm or refute this view, but the index may well prove to be of most value to experienced physicians who see cases of thyroid disease relatively infrequently.

The difficulty of obtaining a precise expression of clinical severity in thyrotoxicosis has complicated previous attempts to correlate its degree with objective measures of thyroid function. Goodwin, Macgregor, Miller, and Wayne (1951), however, classified their cases, on clinical impressions, into four grades, from mild and borderline to severe, and found a rough correlation between the four-hour and 24-hour uptake of radioiodine and clinical severity. No such correlation was found in the case of the 48-hour protein-bound radioiodine. Fraser (1953) has stated that the correlation of the urinary excretion tests with clinical severity is poor. He suggested, however (Fraser, Hobson, Arnott, and Emery, 1953), that one reason for this finding might be that when the *T* index is well above the normal range it increasingly underestimates the thyroid uptake of radioiodine. The clinical index is a measure of severity, in so far as it indicates the number of target-tissue effects. The weightings allotted to individual features ensure, moreover, that emphasis is placed on those phenomena, such as heat intolerance, which are the more reliable indices of abnormality. It is thus possible to plot this measure of clinical severity against the results of radioiodine studies. It can be seen from Figs. 5 and 6 that a significant correlation was found between the degrees of severity as reflected by the indices and by the values of both four-hour uptake and 48-hour protein-bound radioiodine. It must be admitted, however, that if the weighting factors making up the clinical index had been modified so as to express the degree of abnormality of individual clinical features, for example, if different weightings had been given to different grades of tachycardia and loss of weight, the correlation might have been better.

Means (1916) suggested, and Fraser, Hobson, Arnott, and Emery (1953) agreed, that the basal metabolic rate is the best index of severity of the disease. The clinical index correlates well with the basal metabolic rate (Fig. 4). Foote, Mackenzie, and Maclagan (1952) have shown that a significant correlation exists between the basal metabolic rate and the thigh–neck clearance of ^{131}I in hyperthyroidism. It is, therefore, not surprising to find that the coefficients of correlation which exist between the index and the radioiodine criteria used are similar to that found between the index and basal metabolic rate. These results confirm the view that the clinical index can be used as a measure of severity of the disease. They also raise the possibility of the existence of a continuous gradation of thyroid activity, comparable to that found for blood-pressure levels by Pickering (1955). It should be made clear, however, that in allocating numerical values to the features which contribute to the clinical index, we had in mind weightings which would separate sharply normality from abnormality,

and this method would tend to obscure any continuous gradation of increased thyroid activity lying between the obviously normal and the abnormal. This problem of graded activity is worth further study, although it would involve changing the emphasis placed on the weighting factors. Estimations of non-radioactive protein-bound ^{127}I would probably be the best index of thyroid function with which to correlate such a new index.

Conclusion

In our opinion the clinical diagnostic index is of value in day-to-day practice, and we have come to regard it as a reliable and simple aid to diagnosis. When its application produces a score which falls into the equivocal range, it indicates a case which will be difficult to assess on clinical grounds alone and will need confirmation by special tests. We have found it so reliable that we have been able to reduce our demands on the laboratory services. By removing from the score sheet those features which treatment does not affect, we have been able to devise a therapeutic index, which gives a quantitative measure of response to therapy. This technique will be reported later. The clinical index has enabled us to see why certain cases of suspected thyrotoxicosis give rise to diagnostic difficulty, and our analysis and classification of the responsible features should be of help to those who, like us, have found themselves puzzled by a discrepancy between their clinical impression and laboratory findings. The index makes it possible to minimize the effects of 'observer variation', and also makes it easier to discover the reasons why differences in diagnosis occur. Lastly, it should be stressed that this technique is of more general application, and might with advantage be applied to other diseases. We already know that it is possible to construct a clinical index which is of practical help in the diagnosis of conditions other than thyrotoxicosis. Moreover, the application of the method to diagnostic problems throws much light on the technique of diagnosis, and emphasizes the value of precise clinical observation in modern medicine.

We are grateful to Dr. R. A. Robb, Mitchell Lecturer in Statistics, University of Glasgow, for his advice on the statistical aspects of this work. We are indebted to Miss E. Macdonald for assistance in the radioiodine studies, and to Miss S. Willis for carrying out estimations of basal metabolic rate.

APPENDIX

Clinical Diagnostic Index: Recommendations for Use

Symptoms

Questions requiring only positive or negative replies should be avoided, and special care should be taken to ensure that the initial question about each symptom is not a leading one. Supplementary questions should always be asked, and before a symptom is recorded as present these supplementary questions should confirm or clarify the initial answer. For example, in the case of

temperature preference the patient should be asked first: 'What type of weather do you prefer?' rather than 'Do you prefer cold weather?' A suitable supplementary question would be: 'Do you feel comfortable or uncomfortable in a warm room?' Only symptoms of recent onset or recently increased severity should be recorded, with one exception. If preference for heat is present, irrespective of its duration, it should be regarded as significant, since it is highly unusual in thyrotoxic patients. Where there is any doubt about the presence of a symptom it should not be recorded. Our criteria for individual symptoms are as follows:

Dyspnoea on effort. The age of the patient should be taken into account. The symptom is significant only when it is of recent onset.

Palpitations are significant if they occur at rest or during moderate exercise. The age of the patient is relatively unimportant.

Tiredness refers to a feeling of unusual exhaustion after familiar physical effort, and not to symptoms of psychogenic origin, such as tiredness on first waking in the morning.

Temperature preference is of high diagnostic significance, and the type of preference should be recorded only after supplementary questions have been asked. Suitable questions elicit the presence of discomfort in a warm environment, the habit of sitting away from the fire, and diminished use of hot water bottles.

Excessive sweating refers to both thermal and emotional sweating, and the adjective 'excessive' should be omitted from the initial question.

Nervousness. Questions should be asked about irritability, easy loss of temper, jumpiness, and tenseness. The symptom is recorded only if these manifestations have shown a recent increase.

Increase or decrease of appetite. The question 'How is your appetite?' should be an inquiry as to whether it is regarded as less than normal, normal, or excessive.

Increase or decrease of weight should be definite, recent, progressive, and confirmed both by slackness or tightness of clothing and by the opinion of friends or relatives. If the patient has kept records of weight, an increase or decrease of 7 lb. or more during a period of up to one year should be considered significant.

Signs

The following criteria must be fulfilled before a physical sign is recorded as present:

Palpable thyroid. The gland should be significantly enlarged, and visible as well as palpable, except in male subjects, in whom any palpable thyroid tissue is considered abnormal.

A bruit over the thyroid should be high-pitched, and systolic or to-and-fro, and to distinguish it from a venous hum it should be uninfluenced by rotation of the head or pressure on the neck veins.

Exophthalmos. Sclera should be seen between the lower lid and the iris of one or both eyes, with the patient looking directly ahead.

Lid retraction. Sclera should be seen between the upper lid and the iris of one or both eyes, with the patient looking directly ahead.

Lid lag. An area of sclera should increase or appear when the patient's eyes are fixed on the examiner's finger moving from above downwards. It should be noted that this criterion is more strict than that usually employed.

Hyperkinetic movements. The movements of removing and replacing clothing have to be unusually rapid and jerky, conveying an impression of over-reaction,

wasted energy, and clumsiness. It is the combination of rapidity and inaccuracy of movement which is significant.

Fine finger tremor. With the patient's eyes closed, the outstretched separated fingers should show a fine tremor. Coarse tremor is ignored, but if doubt exists the sign is recorded as present.

Warm, moist hands. The palms are compared with the hands of the examiner, taking into account the temperature of the environment and his normal vasomotor tone. They should be warmer than those of the examiner, and a sensation of dampness should remain on his hands after withdrawal.

Casual pulse rate. This is counted for one minute at the end of the examination.

Summary

1. Analysis of the frequency of symptoms and signs in thyrotoxic patients and normal subjects allows the allocation to each clinical feature of a numerical value which varies with its diagnostic significance. The aggregate score in an individual case is termed the 'clinical diagnostic index', and has been derived in 99 unquestionably non-toxic and 83 unquestionably thyrotoxic subjects. The values attached to individual signs and symptoms have then been modified to minimize the effects of 'observer variation' and to produce the greatest possible separation between the two groups, so that all non-toxic subjects had indices of less than +11 and all toxic subjects greater than +19.

2. The method was then applied to 118 cases which had presented initial diagnostic difficulty, using the weighting factors for clinical features established by the study of the definitely non-toxic and toxic cases. The clinical diagnostic indices produced good separation between cases finally shown to be non-toxic and those shown to be toxic. Fifty-nine of 67 non-toxic cases (88 per cent.) had scores less than +11, seven (10·5 per cent.) lay within the range +11 to +19, which is called the 'equivocal range', and one (1·5 per cent.) fell in the toxic range. Forty-five (88 per cent.) of the 51 toxic cases had scores greater than +19, and the remaining six cases all fell within the equivocal range.

3. 'Observer variation' studies showed no statistically significant difference between the scores obtained independently by experienced observers.

4. The diagnostic accuracy of the method was not significantly different from that of radioiodine studies and estimations of basal metabolic rate.

5. The method has been applied in four different centres to 171 patients, and the diagnostic accuracy (85 per cent.) was similar to that obtained in the original series of cases.

6. Examination of individual features making up the index often explains the mechanism by which a clinical diagnosis has been reached, and makes it clear why in certain cases diagnostic difficulty has been found.

7. The scores can be used as indices of severity in toxic subjects, and significant correlations existed between the scores and the four-hour uptake of radioiodine, the 48-hour plasma protein-bound radioactivity, and the basal metabolic rate.

REFERENCES

Ansell, G., Macgregor, A. G., Miller, H., and Wayne, E. J. (1953) *Radioisotope Techniques*, **1**, 52. H.M.S.O. London.

Bauer, R. E. (1956) *Ann. intern. Med.* **44**, 207.

Bortin, M. M., Silver, S., and Yohalem, S. B. (1951) *Amer. J. Med.* **11**, 40.

Cochrane, A. L., Chapman, P. J., and Oldham, P. D. (1951) *Lancet*, **1**, 1007.

Crooks, J., Murray, I. P. C., and Wayne, E. J. (1958) Ibid. **1**, 604.

Fletcher, C. M. (1952) *Proc. roy. Soc. Med.* **45**, 576.

Foote, J. B., Mackenzie, D. H., and Maclagan, N. F. (1952) *Lancet*, **1**, 486.

Fraser, T. R. (1953) *Memoirs of the Society for Endocrinology*, No. 1, *The Thyroid Gland*, p. 36. London.

—— Hobson, Q. J. G., Arnott, D. G., and Emery, E. W. (1953) *Quart. J. Med.* N.S. **22**, 99.

Glaser, E. M., and Whittow, G. C. (1954) *Clin. Sci.* **13**, 199.

Goodwin, J. F., Macgregor, A. G., Miller, H., and Wayne, E. J. (1951) *Quart. J. Med.* N.S. **20**, 353.

Macgregor, A. G., and Wayne, E. J. (1957) *Modern Trends in Endocrinology*. London.

Means, J. H. (1916) *Boston med. surg. J.* **174**, 864.

Oyama, T., and Tatsuoka, M. (1956) *Amer. Rev. Tuberc.* **73**, 472.

Pickering, G. (1955) *High Blood Pressure*. London.

Rao, C. R. (1948) *J. roy. Stat. Soc.* B, **10**, 159.

Robertson, J. D., and Reid, D. D. (1952) *Lancet*, **1**, 940.

Schilling, R. S. F., Hughes, J. P. W., and Dingwall-Fordyce, I. (1955) *Brit. med. J.* **1**, 65.

Schultz, A. L., and Zieve, L. (1956) *Amer. J. Med.* **20**, 30.

Skanse, B. (1949) *Acta med. scand.* Suppl. **235**, 1.

Wayne, E. J. (1954) *Brit. med. J.* **1**, 411.

Williams, R. H. (1950) *Textbook of Endocrinology*, London.

Zieve, L., and Hill, E. (1955*a*) *Gastroenterology*, **28**, 759.

—— —— (1955*b*) Ibid. **28**, 785, 914.

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COMPULSIVE WATER DRINKING[1]

By E. D. BARLOW and H. E. DE WARDENER

(From the Departments of Psychological Medicine and Medicine, St. Thomas's Hospital Medical School)

Severe polydipsia and polyuria without glycosuria may be due to (1) renal disease, including the renal complications of potassium deficiency and hypercalcaemia, (2) compulsive water drinking, or (3) diabetes insipidus. In general, the diagnosis of renal disease is easy, and the principal diagnostic difficulty is to distinguish diabetes insipidus from compulsive water drinking. The distinction is usually based on the clinical history and appearance of the patient, and on the interpretation of certain investigations which are intended to test the functional integrity of the neurohypophysis. The purpose of the present paper is to describe the clinical features and certain physiological disturbances of nine patients with compulsive water drinking. The diagnosis from diabetes insipidus (14 patients) is then discussed. Compulsive water drinking is defined as an excessive consumption of fluid due to psychological disturbance, and diabetes insipidus as a persistent defect in the ability to secrete antidiuretic hormone (ADH).

Clinical Features of Compulsive Water Drinking

There were seven women and two men; their ages, except for one patient of 24, ranged from 48 to 59 years (Table I). Three case histories are given in the Appendix (Nos. 2, 4, and 7). Detailed psychiatric histories were obtained in seven patients (Nos. 1, 2, 4, 5, 7, 8, and 9).

Past history

Personal history. Neurotic traits were common in childhood; a history of instability and vague illness during early years was obtained in all seven patients from whom a psychiatric history was obtained, and five of these had walked in their sleep. Schooling had often been interrupted, and adolescence had not been smooth. Work histories, on the other hand, were very variable, and several patients had achieved positions of stability and responsibility, in spite of frequent interruptions through illness. All patients had had episodes of time off work through illness, or frequent or unexplained changes of work. No patient had a history of a stable and satisfactory sex life. Their difficulties included menstrual disturbances since puberty and many gynaecological operations (for example, patient No. 8, who also had premenstrual aphonia). Six patients had married; subsequently there had been many discordant and unhappy episodes,

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and separation in several cases. The patients had abstemious habits, except for a few who smoked heavily.

Family history. One patient (No. 4) had an aunt who was a dipsomaniac, and his father was said to have had diabetes insipidus; the father of patient No. 2 had become an alcoholic at the age of 47; one patient (No. 8) had a sister with an even more florid medical history than herself.

Medical history. This was usually dramatically given, and often enough contained truly dramatic episodes. Most patients (seven out of nine) attended one or more hospitals frequently, for both psychological and organic illness. Some admissions were for emergencies (for example, abdominal pain simulating intestinal obstruction or peritonitis) which turned out to be false alarms. Often the patient omitted to mention that recovery had occurred without treatment (Nos. 1 and 8). On the other hand, many operations were performed, as in patient No. 2, who had six operations between the ages of 33 and 49. Eight patients had a history of previous psychological disturbances. This was often revealed in the routine examination; sometimes it was withheld, as by patient No. 1, who did not mention that she had been admitted to a mental hospital. Six patients (Nos. 1, 2, 5, 7, 8, and 9) had a history of hysterical episodes, including paralysis, aphonia, pyrexia artefacta, pseudocyesis, and 'stocking' anaesthesia; two patients (Nos. 4 and 5) had had delusional hypochondriasis; three (Nos. 2, 5, and 9) had been depressed; two (Nos. 1 and 2) had been found pouring jugs of water into the bed-pan at other hospitals. In addition, three patients (Nos. 3, 7, and 9) had had changes of weight which suggested that they had suffered from compulsive eating.

Present illness

Compulsive drinking had been present for periods of from four months to 20 years (Table I). The onset was sudden in one patient (No. 8), in whom it was clearly a hysterical conversion. In most of the others the history of onset was vague, and occurred during the menopause (Nos. 1, 2, and 5), during a delusional illness (Nos. 4 and 5), and in periods of depression (Nos. 2, 4, 5, and 9). In two patients (Nos. 7 and 9) it coincided with domestic stress. Patients Nos. 1, 4, and 7 attributed the onset to some definite event—a husband's death, morphine addiction, and the wearing of an abdominal belt. One patient (No. 6) considered that drinking up to five litres a day was normal. In seven of the nine patients (Nos. 1 to 5, 7, and 9) the intake of fluid fluctuated irregularly from hour to hour or from day to day; frequently a great deal more was drunk when the patient was the centre of attention or apprehensive, for example, before the start of an investigation. If fluid was not accessible most patients became agitated, except during the fluid deprivation tests. Some patients had periodic remissions and relapses lasting several months or longer. Patients Nos. 2 and 7 did not specifically complain of thirst and polyuria, though they admitted to these symptoms on direct questioning; patient No. 6 did not think that he was abnormally thirsty. Relapses were sometimes precipitated by domestic stress (Nos. 1, 2, 7, and 9), or by an acute illness (Nos. 2 and 3).

Condition on examination. All the patients looked well except No. 4. They gave the appearance of being co-operative, even when they were reticent about their past psychiatric histories, or were subsequently discovered pouring water into the bed-pan (Nos. 1, 3, and 8). The observed psychological disturbances ranged from severe delusions (Nos. 4 and 5), depression (Nos. 4, 5, 7, 8, and 9), or agitation (No. 2), to frank hysterical behaviour (Nos. 1, 2, 8, and 9) including *belle indifférence*, tunnel vision, unilateral ptosis, and facial mannerisms. A detailed psychological history was not obtained from patient No. 6, but on routine observation in the ward he appeared normal. The volume of urine passed during 24 hours varied from 2·5 to 5 litres in No. 6 to 13 to 20 litres in No. 2. The amount passed during the day was usually more than during the night, and the total volume was apt to fluctuate widely from day to day; it increased suddenly when the patient was apprehensive. The blood urea varied from 22 to 18 mg. per 100 ml., and the creatinine clearance from 188 to 63 ml. per minute. Proteinuria was found only in patient No. 4, who had a diseased bladder (see Appendix). There were few abnormal physical signs, and the visual fields and skull X-rays did not reveal any evidence of structural lesions in the region of the pituitary. In four patients (Nos. 1, 4, 8, and 9) the blood-pressure was raised and fluctuated, sometimes violently, for example, from 180/100 to 300+/185 (patient No. 1). Three patients were obese (Nos. 3, 7, and 9) and one of these (No. 3) was hirsute. Organic abnormalities were present in three other patients: multiple papillomata of the bladder (No. 4), peptic ulcer (No. 6), and minor residual effects of a cerebral vascular accident which had occurred eight years previously, after the onset of compulsive drinking (No. 2).

Physiological Disturbances in Compulsive Water Drinking

The normal subjects mentioned below were medical students and doctors.

A. *Plasma osmolality*

Method

Venous blood was obtained from an antecubital vein, immediately before the start of one of the other investigations. The patients were given two to three hours' warning that an investigation was about to be performed, but no attempt was made to influence the consumption of fluid. The blood was centrifuged, and the plasma osmolality (m-osmoles per kg.) estimated from the freezing-point depression measured with a thermistor (de Wardener and del Greco, 1955).

Results (Fig. 1)

The mean osmolality in compulsive water drinkers was lower than in normal subjects. In eight compulsive water drinkers it was 269±14 m-osmoles per kg., with a range from 239 to 288 m-osmoles per kg.; in 14 normal subjects it was 280±6 m-osmoles per kg., with a range from 273 to 289 m-osmoles per kg.: a difference which is significant at less than the 1 per cent. level.

B. *Ability of the kidney to concentrate the urine in response to intravenous vasopressin*

As compulsive water drinking is due to a disturbed mental state, it seems

reasonable to suppose that the ability of the kidney to concentrate the urine after intravenous vasopressin would be normal. It has been found, however, that the kidney's ability to concentrate varies considerably, and occasionally may be severely impaired.

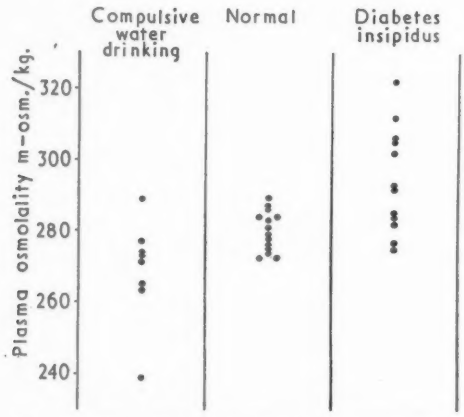

FIG. 1. The plasma osmolality in compulsive water drinking, in normal subjects, and in diabetes insipidus.

Method

A catheter was placed in the bladder, and one or more of the following tests were performed: (1) The effect of a single intravenous injection of 100 to 200 m-units of aqueous vasopressin. (2) The effect of an initial dose of 100 to 200 m-units of aqueous vasopressin, followed by a continuous infusion of 5 m-units per minute for one hour. (3) The effect of continuing the vasopressin infusion, and at the same time inducing an osmotic diuresis: the administration of vasopressin was continued at the same rate, while 300 to 500 ml. of 25 per cent. mannitol were given at a rate of 10 ml. per minute.

Every patient knew that a test was to be performed, but no fluid restrictions were imposed before its onset. If the excessive intake of water continued unabated after vasopressin had reduced the flow of urine, the patient was persuaded to diminish his intake until the effect of the vasopressin had ceased.

Results

(1) *Single intravenous injection of vasopressin.* Fig. 2 shows the effect in patient No. 8 compared with a normal person; in the latter vasopressin was given during an induced water diuresis of one hour's duration. It is evident that the patient had a severe impairment of the ability to concentrate.

(2) *Single intravenous injection of vasopressin followed by continuous infusion.* The results are shown in Table I and illustrated in Fig. 3. The urine concentration in compulsive water drinking was usually less than in normal subjects. The highest urine concentration achieved in eight compulsive water drinkers

varied from 233 to 734 m-osmoles per kg.; in nine normal subjects it varied from 590 to 1,016 m-osmoles per kg.

(3) *Mannitol osmotic diuresis during a continuous intravenous infusion of vasopressin.* The decreased ability to concentrate the urine in some of the patients

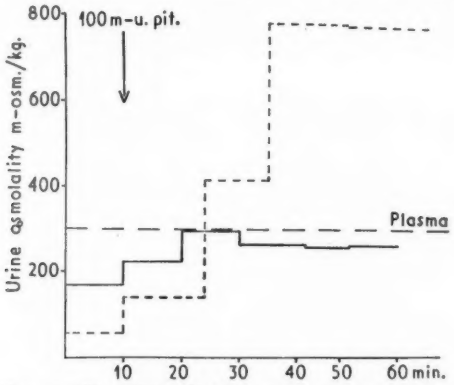

FIG. 2. The effect of 100 m-units of intravenous aqueous vasopressin (pit.) in a compulsive water drinker (————), and in a normal subject one hour after ingestion of one litre of water (– – – –).

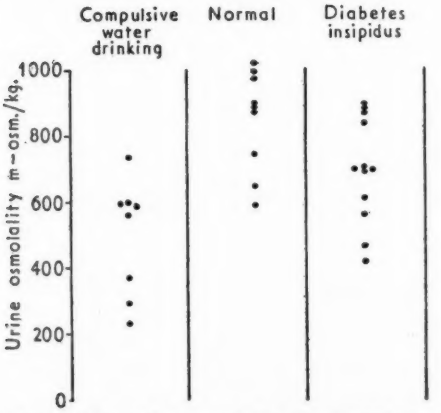

FIG. 3. The urine osmolality in compulsive water drinking, in normal subjects, and in diabetes insipidus, after intravenous aqueous vasopressin.

with compulsive water drinking was associated with a raised output of solutes (Table I) due to a transient salt diuresis. In order to distinguish whether the inability to concentrate was due to the raised solute output, or to an impaired ability of the tubules to respond to vasopressin, observations were made of three patients' ability to concentrate with vasopressin over a large range of solute output, and the results compared with those obtained in two normally hydrated subjects. Fig. 4 shows that over a wide and identical range of solute output the

concentration of the patients' urine was always lower than in the normal subjects. It follows that a considerable part of the impairment in the ability to concentrate in the patients with compulsive water drinking was unrelated to the rate of solute output, and therefore that there was an impaired ability of the tubules to respond to vasopressin.

C. *Ability of the neurohypophysis to secrete ADH in response to fluid deprivation and nicotine*

The evidence in this section shows that though most patients with compulsive water drinking secrete ADH normally, some have a transient impairment.

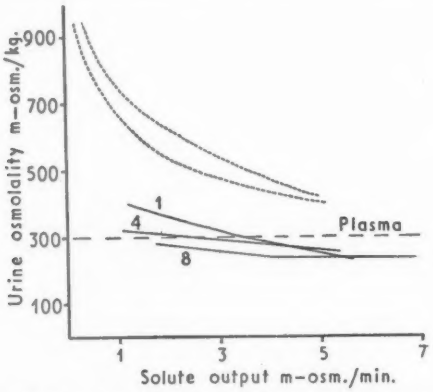

FIG. 4. The effect on urine osmolality of intravenous mannitol and vasopressin in three cases (Nos. 1, 4, and 8) of compulsive water drinking (———) and in two normal subjects (– – – –). The initial (control) solute output in the compulsive water drinkers was greater than in the normal subjects because of an increased salt excretion, but over a wide and identical range of solute output the concentration of the urine was always lower in the compulsive water drinkers.

Fluid deprivation. As ADH cannot be estimated in the blood, the effect of fluid deprivation on ADH secretion has to be inferred from changes in urine flow or urine concentration. Such changes, however, are related not only to ADH secretion but also to the kidney's ability to respond to ADH, and the rate of solute output. During fluid deprivation in normal subjects the tubules are saturated with ADH, for at this time an injection of vasopressin causes no further increase in the concentration of the urine (Jones and de Wardener, 1956). It follows that before it is possible to interpret the effect of fluid deprivation on ADH secretion the response of the kidneys to a saturating dose of administered vasopressin must be known, and the output of solute during both fluid deprivation and vasopressin administration must be similar.

In normal subjects the concentration of the urine following fluid deprivation is greater than after vasopressin, while the solute output is slightly less. If, therefore, in a patient with polydipsia and polyuria the urine concentration is greater after fluid deprivation than after vasopressin, it is reasonable to infer that fluid deprivation has stimulated the secretion of large quantities of ADH,

however low the urine concentrations achieved. Conversely, if the urine concentration after fluid deprivation is substantially less than after vasopressin, it is assumed that fluid deprivation has failed to stimulate a normal secretion of ADH, *however high the urine concentrations* achieved. These assumptions are valid only if the solute output is the same or slightly less with fluid deprivation than with vasopressin, that is, if the changes in solute output are similar to those that occur in normal subjects.

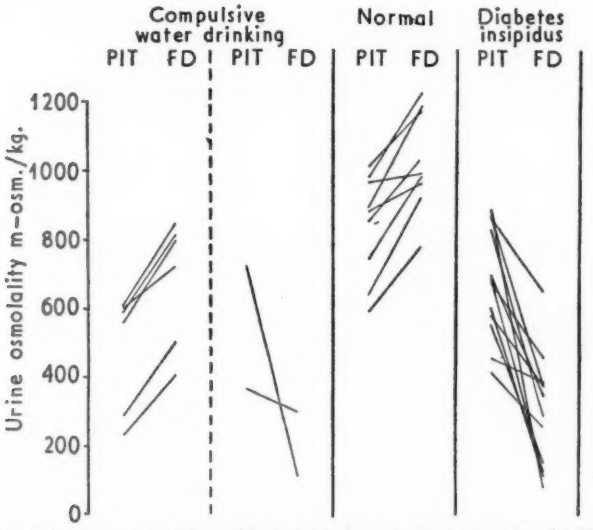

FIG. 5. The urine osmolality after intravenous aqueous vasopressin (PIT) and after fluid deprivation (FD) in compulsive water drinking, in normal subjects, and in diabetes insipidus; each line represents one subject.

Nicotine. ADH secretion is stimulated by nicotine. The presence of ADH has again to be surmised from changes which take place in urine concentration or urine flow when compared with those obtained after the administration of vasopressin. But the comparative effects of vasopressin and nicotine on the ability to concentrate the urine has not been studied extensively in normal subjects. In three normal subjects we have found that the concentration after nicotine is about the same as after vasopressin. It follows that the ability of the neurohypophysis to secrete ADH after an injection of nicotine is assessed according to the same criteria as after a period of fluid deprivation, except that it is not necessary for the urine concentration to be greater than that obtained after vasopressin for there to be good presumptive evidence that large quantities of ADH have been secreted.

Methods

Fluid deprivation. The intake of all fluids, including ice cream, soup, and fruit, was stopped for 24 hours, or until more than 3 per cent. of the initial body weight had been lost. The duration of fluid deprivation, the loss of weight, the volume of

TABLE I

Compulsive Water Drinking

Case number	*Associated psychiatric abnormalities*	*Sex*	*Weight (kg.)*	*Age (years)*	*Duration of polydipsia (years)*	*Plasma osmolality (m-os-moles/kg.)*	*Vasopressin test*		*Fluid deprivation test*					
							Urine osmolality (m-os-moles/kg.)	*Urine flow (ml./min.)*	*Duration (hours)*	*Loss of weight (kg.)*	*Urine excreted (ml.)*	*Change in plasma osmolality (m-os-moles/kg.)*	*Urine osmolality (m-os-moles/kg.)*	*Urine flow (ml./min.)*
1	Conversion hysteria. Depression	F	49	48	2	271	372	3·2	12	3·4	2,750	+32	301	1·8
2	Conversion hysteria. Depression	F	77	57	11	265	734	0·87	12	3·2	2,038	+19	113	1·44
3	Hysteria. Bulimia	F	74	24	6	288	587	1·6	24	1·7	1,130	+5	725	1·0
4	Delusional hypochondriasis. Depression	M	58	56	3	263	289	3·6	32	..	2,220	..	505	1·16
5	Delusional hypochondriasis. Depression. Hysteria	F	50	53	1	277	560	1·33	32	1·8	1,145	..	806	0·42
6	None	M	73	53	?	273	597	0·63	32	..	1,200	+11	822	0·19
7	Hysteria. Depression. Bulimia	F	108	51	$\frac{7}{12}$	274	602	0·62	24	..	1,340	..	850	0·32
8	Conversion hysteria. Depression	F	50	59	$\frac{4}{12}$	239	233	7·3	24	..	2,500	+13	413	1·8
9	Hypochondriasis. Hysteria. Depression	F	86	55	20	..	..	..	..	..	..	..	..	..

TABLE II

Diabetes Insipidus

Case number	*Cause of diabetes insipidus*	*Sex*	*Weight (kg.)*	*Age (years)*	*Duration of polydipsia (years)*	*Plasma osmolality (m-osmoles/kg.)*	*Vasopressin test*		*Fluid deprivation test*					
							Urine osmolality (m-osmoles/kg.)	*Urine flow (ml./min.)*	*Duration (hours)*	*Loss of weight (kg.)*	*Urine excreted (ml.)*	*Change in plasma osmolality (m-osmoles/kg.)*	*Urine osmolality (m-osmoles/kg.)*	*Urine flow (ml./min.)*
1	Unknown. Associated with cerebellar disease	M	55	18	11/12	293	695	0·24	7	2·7	2,465	+22	146	3·42
2	Eosinophilic granuloma	M	37	12	3/52	..	874	0·30	24	2·5	?	..	665	0·37
3	Chicken pox	F	30	9	6	285	867	0·28	6	1·25	1,025	..	378	1·57
4	Secondary carcinoma; primary in larynx	M	71	62	3/12	284	611	0·71	12	4·4	3,925	+34	117	0·55
5	Unknown	F	55	45	16	302	834	0·73	24	2·7	2,150	..	298	1·3
6	Secondary carcinoma; primary in bronchus	M	79	56	3/12	306	420	1·34	17	2·7	2,350	+12	252	1·8
7	Unknown	M	77	49	5	292	702	0·73	30	3·1	2,850	..	356	0·92
8	Unknown	F	52	21	14/52	312	589	0·89	24	3·2	2,960	+12	380	0·77
9	Neurohypophyseal destruction by radioactive gold for carcinomatosis	F	39	72	3/12	282	463	0·90	20	2·2	1,990	+13	394	0·96
10	Unknown	F	42	79	3/12	277	563	0·43	16	2·3	1,940	+19	179	1·33
11	Optic glioma	M	38	15	11/12	..	890	0·24	4	1·3	900	..	80	2·8
12	Leukaemic infiltration of neurohypophysis	F	72	60	3/52	275	693	0·82	22	3·2	2,230	+12	468	0·66
13	Eosinophil granuloma	M	72	23	4	305	..	..	..	..	..	..	..	..
14	Craniopharyngioma	F	40	16	9/12	322	..	..	..	..	..	..	..	..

urine passed during this period, and the changes which occurred in plasma osmolality are given in Tables I and II.

Nicotine. Nicotinic acid tartrate, 3 to 6 mg., was given intravenously at a time when the fluid intake was uninhibited. The test was performed in two compulsive water drinkers, and the rate of administration was sufficient to cause intense nausea, vomiting, and profuse sweating.

Results (Fig. 5; Tables I and II)

Fluid deprivation. In both compulsive water drinkers and normal subjects the solute output was slightly less with fluid deprivation than with vasopressin.

(1) In *compulsive water drinking* the concentration of the urine after fluid deprivation varied from 113 to 850 m-osmoles per kg. In six patients (Nos. 3 to 8) the urine concentration after fluid deprivation was *greater* than after vasopressin by 138 to 248 m-osmoles per kg., and it is concluded that these patients had no defect in neurohypophyseal function, although in two the urine concentrations after fluid deprivation were only 505 and 413 m-osmoles per kg. (urine osmolalities which correspond to specific gravities of about 1,015 and 1,012). In the other two patients (Nos. 1 and 2) the urine concentrations after fluid deprivation were *less* than after vasopressin by 71 and 621 m-osmoles per kg., though fluid deprivation in both caused a substantial fall in weight and rise in plasma osmolality (Table I). It is concluded that at this time these two patients had a defect of neurohypophyseal function. This conclusion is supported by the fact that in both instances the administration of intravenous vasopressin at the end of the period of fluid deprivation immediately raised the concentration of the urine to a value greater than when it was given during a period of uninhibited water drinking. After treatment both patients were able to concentrate urine normally after a less severe deprivation of fluid.

(2) In *normal subjects* the concentration of the urine after fluid deprivation was 791 to 1,230 m-osmoles per kg.; in all subjects this concentration was greater than that obtained with vasopressin, the differences ranging from 24 to 300 m-osmoles per kg.

Nicotine. The two patients (Nos. 1 and 8) who were given nicotine had previously been shown to have a severe impairment in their ability to concentrate the urine in response to vasopressin. After the injection of nicotine the concentration of the urine rose to about the same values as after vasopressin. In patient No. 8 it rose to 258 m-osmoles per kg., which was 25 m-osmoles per kg. greater than after vasopressin; in patient No. 1 it rose to 295 m.-osmoles per kg., which was 77 m-osmoles per kg. less than after vasopressin. It is concluded that the neurohypophysis in patient No. 8 was able to secrete large quantities of ADH, a conclusion similar to that obtained with fluid deprivation. The result in patient No. 1 is equivocal; she was one of the patients in whom urine concentration after fluid deprivation was less than after vasopressin, and in whom it had therefore been concluded that there was an impaired ability to secrete ADH in response to fluid deprivation.

D. *Response to long-acting vasopressin*

When patients with compulsive water drinking were given five units of vasopressin tannate in oil, the rate of urine flow decreased, even though the ability to concentrate was severely impaired. But they continued to feel insatiably thirsty, drank large quantities of water, and tended to develop the clinical

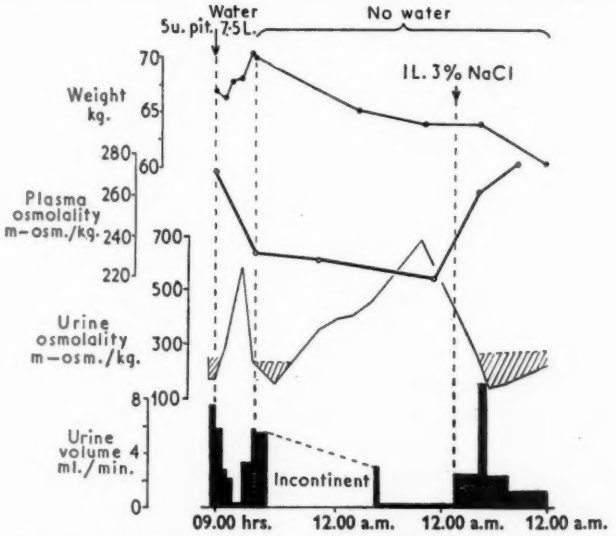

FIG. 6. The effect of vasopressin tannate in oil (pit.) on a compulsive water drinker (patient No. 2). Urine flow decreased, but the patient continued to drink large volumes of water, and in seven hours she gained 3·5 kg. (•—•) in weight and the plasma osmolality (o—o) fell from 272 to 232 m-osmoles per kg. Initially the urine was hypotonic (hatched area), and it then became hypertonic. At the peak of the gain of weight after seven hours the urine became hypotonic, and its volume increased; the patient vomited, became incontinent, developed a hysterical fugue, and stopped drinking. A few hours later urine became hypertonic once more, and remained so for the next two days, so that the plasma osmolality continued to fall though the weight returned towards normal. On the third day one litre of 3 per cent. saline given intravenously raised the plasma osmolality from 218 to 275 m-osmoles per kg., and induced a brisk diuresis of hypotonic urine.

features of over-hydration. Headache, nausea, and vomiting, a sense of abdominal fullness, and a tightness of the skin, were associated with bad-tempered querulousness and a feeling of unreality. Sometimes they objected violently to the vasopressin tannate, and refused further injections. A typical comment was 'I have no use for pitressin because it does not stop the thirst; instead of 30 pints a day I drink 18, but I feel blown up and horrible'. Fig. 6 illustrates the effect of an injection of five units of vasopressin tannate in oil on patient No. 2, whose ability to concentrate the urine with vasopressin was normal (Table I). After the injection she continued to drink enormous volumes of water, though the urine flow fell below 0·5 ml. per minute; in seven hours she gained 3·5 kg. in weight, and lowered her plasma osmolality from 272 to 232 m-osmoles per kg. She then vomited, became incontinent, appeared to lose

consciousness, and developed a hysterical fugue (see Appendix); water drinking ceased for the next 60 hours.

Diagnosis between Compulsive Water Drinking and Diabetes Insipidus

Compulsive water drinking is usually distinguished from diabetes insipidus by testing the integrity of the neurohypophyseal system. The methods used include the response of the urine flow or concentration to fluid deprivation, intravenous nicotine, and hypertonic saline. We have used fluid deprivation, and interpreted the result in conjunction with a test of the kidney's capacity to concentrate the urine after intravenous aqueous vasopressin, as described in Section B above. An estimation of the plasma osmolality and the effect of long-acting vasopressin have also been found useful in distinguishing the two conditions.

A summary of the results obtained in 14 patients with diabetes insipidus is given below, and compared with the results found in patients with compulsive water drinking and normal subjects. The particulars of the patients with diabetes insipidus are given in Table II; they all felt better on prolonged treatment with vasopressin tannate in oil, and in six there was evidence, at operation or *post mortem*, of structural damage to the neurohypophysis.

Ability of the neurohypophysis to secrete ADH in response to fluid deprivation (see Sections B and C for methods). The ability of patients with diabetes insipidus to concentrate the urine with aqueous vasopressin is shown in Table II and Fig. 3. In some patients the ability to concentrate was impaired; the range of concentration in 12 patients was 420 to 890 m-osmoles per kg. Nevertheless, in contrast to six of the eight patients with compulsive water drinking and all the normal subjects, the concentration obtained after fluid deprivation was always *less* than with vasopressin (the changes in solute output were similar in all three groups) (Table II; Fig. 5). The differences ranged from 69 to 810 m-osmoles per kg. It is concluded that all these patients had a defect of neurohypophyseal function, though in two the urine concentration after fluid deprivation was as high as 665 and 468 m-osmoles per kg. (urine osmolalities which correspond to specific gravities of 1,018 and 1,014).

Plasma osmolality (see Section A for method). The mean plasma osmolality in diabetes insipidus was higher than in normal subjects, and was thus much greater than in compulsive water drinking (Table II; Fig. 1). In 12 patients with diabetes insipidus it was 295 ± 15 m-osmoles per kg., with a range of 275 to 322 m-osmoles per kg. The statistical differences between this group and both the normal group and the patients with compulsive water drinking were significant at less than the 1 per cent. level.

The effect of long-acting vasopressin sometimes provided the best distinction between compulsive water drinking and diabetes insipidus. In both conditions the administration of five units of vasopressin tannate in oil slowed the urine flow, even though the ability to concentrate the urine might be severely impaired. Soon after the injection patients with diabetes insipidus were relieved of their thirst, and thankfully cut down their fluid intake; in contrast, patients

with compulsive water drinking continued to drink, and were liable to become ill from over-hydration.

Treatment of Compulsive Water Drinking

Three patients had spontaneous remissions, either before (No. 9) or soon after admission (Nos. 5 and 7). In two (Nos. 5 and 9) remission occurred for no apparent reason; in the third (No. 7) it coincided with an attack of acute abdominal pain and vomiting. Two patients were treated with continuous narcosis (Nos. 1 and 2), and two with electroconvulsive therapy (Nos. 4 and 8); in all four this

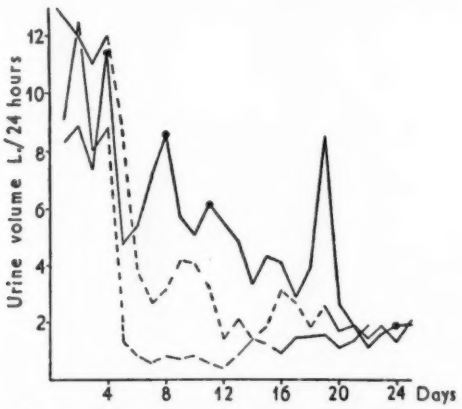

FIG. 7. The effect on the daily urine volume of electroconvulsive therapy (•) in patient No. 4, and of continuous narcosis (----) in Nos. 1 and 2. The uninterrupted lines represent the urine output when the patient was awake and drinking to satisfaction.

treatment was followed by a remission of the thirst and polyuria, and a general improvement in mood. The effect on the urine volume in three of the patients is illustrated in Fig. 7; nevertheless, three patients had a relapse of polydipsia and polyuria a few weeks to a few months later. The fourth (No. 2) has had a remission for two years. Patient No. 1, who relapsed after continuous narcosis, was later given a course of electroconvulsive therapy, but again the effect was only transient. One patient (No. 3) was treated with reassurance, but with little effect.

Discussion

There are 10 recorded cases of compulsive water drinking (Hickey and Hare, 1944; Carter and Robbins, 1947; Cates and Garrod, 1951; Dingman, Benirschke, and Thorn, 1957; Kleeman, Maxwell, and Witlin, 1958); in these papers 23 cases of diabetes insipidus are also discussed. To compare the age and sex incidence of the two conditions, these cases have been added to those described here, making a total of 19 cases of compulsive water drinking and 37 of diabetes insipidus. Of the 19 compulsive water drinkers 79 per cent. were women, the distribution between male and female patients being the same in our patients

as in the published reports. The age at onset was between eight and 18 years in four patients, and between 35 and 59 years in 14; in one it was uncertain. These findings suggest that adolescence and involution are precipitating factors in compulsive water drinking. In comparison, only 41 per cent. of the patients with diabetes insipidus were female, and the incidence was greatest before the age of 20 (Figs. 8 and 9).

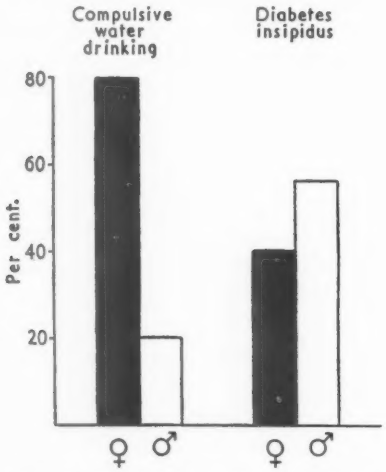

FIG. 8. The sex incidence of compulsive water drinking and diabetes insipidus.

It is customary and reasonable to consider that compulsive water drinking occurs in emotionally disturbed people (Dingman, Benirschke, and Thorn, 1957), but there is little published evidence of their psychological state. In some accounts it is not discussed. In others there is a brief mention of disturbances similar to those we have described—facial mannerisms (Kleeman, Maxwell, and Witlin, 1958), and compulsive eating (Carter and Robbins, 1947; case L. G.). In three patients there is clear evidence of associated psychiatric conditions; Cates and Garrod (1951) described one (patient M. T.) with recurrent abdominal complaints and pyrexia artefacta. Dingman, Benirschke, and Thorn (1957) described two others; the first (Case No. VIII) had polydipsia, hypomania, and craving for sexual activity, cigarettes, and coffee; the second (Case No. IX) had a cyclical psychosis, in which the polydipsia coincided with anxiety. In addition to compulsive water drinking, eight of the nine patients whom we report had definite evidence of psychological disturbance, ranging from severe psychosis to minor neurotic behaviour. Some patients had long histories of severe personality disorders, but had nevertheless lived useful lives. Hysterical episodes were common both in the past and in hospital. Three patients were discovered pouring water into the bed-pan, and one of these three also produced pyrexia artefacta. Several patients were untruthful and evasive when giving their histories, and a few did not mention their excessive thirst and polyuria

until directly questioned. In most patients there were large fluctuations in the amount of water consumed; big changes were often observed from hour to hour and from day to day; sometimes fluid intake was normal for several months or years.

The finding that the plasma osmolality in compulsive water drinking is less than in normal subjects, but that it is greater than normal in diabetes insipidus, has not previously been described; it is in accord with the basic difference between the two conditions. In compulsive water drinking the initial disturbance is excessive drinking, and polyuria is the normal response to expansion and

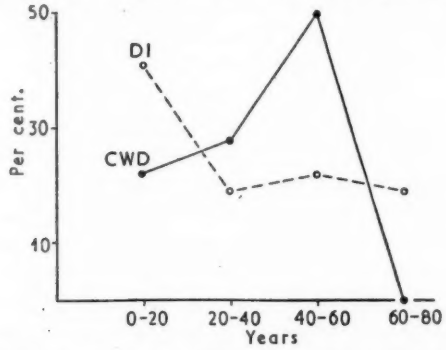

FIG. 9. The age distribution of compulsive water drinking (CWD) and diabetes insipidus (DI).

dilution of body fluids. In diabetes insipidus the initial disturbance is polyuria, and the excessive drinking is a normal response to contraction and concentration of body fluids. It follows that in compulsive water drinking the plasma osmolality will tend to be low, whereas in diabetes insipidus it will tend to be high. It must be stressed that plasma osmolalities were measured on blood obtained at the start of an investigation, and that all the subjects knew that the investigation was about to take place. In normal subjects and patients with diabetes insipidus this knowledge had no noticeable effect on their intake of fluid, but in patients with compulsive water drinking it often caused a striking increase. It is possible, therefore, that the observed plasma osmolality in compulsive water drinking was lower than if the blood had been taken when the patients were not apprehensive. Nevertheless this cannot be the only cause of the low values, for in patients Nos. 1 and 8 the plasma osmolality of blood taken without previous warning was similar to that obtained on the former occasion. It is concluded that if the plasma osmolality, in a case of polyuria and polydipsia without glycosuria or renal disease, is less than 275 m-osmoles per kg., the diagnosis is likely to be compulsive water drinking, and if it is greater than 290 m-osmoles per kg. it is likely to be diabetes insipidus.

It was surprising to find that in both compulsive water drinking and diabetes insipidus the ability to concentrate the urine in response to administered vasopressin is sometimes severely impaired. In three compulsive water drinkers the maximum osmolality obtained was 233, 289, and 372 m-osmoles per kg.

Similarly the osmolality did not rise above 300 m-osmoles per kg. in the patient described by Kleeman, Maxwell, and Witlin (1958). In our patients this decreased ability to concentrate was due in part to a raised solute output, presumably due to the emotional effect of the test (Miles and de Wardener, 1953), but the principal cause was a diminished ability of the tubules to respond to vasopressin (Fig. 4). The cause of this diminution is unknown. When water drinking remitted, the ability to concentrate returned towards normal. It seems reasonable to suppose, therefore, that this change in tubular function is related directly to the large amounts of water ingested. De Wardener and Herxheimer (1957) have demonstrated that the ability to concentrate the urine with both vasopressin and fluid deprivation is severely impaired after drinking about 10 litres of water per day for 11 days; and Epstein, Kleeman, and Hendrikx (1957) have obtained similar changes after three days' increased water intake. Nevertheless this explanation is not completely satisfactory, for the impairment of concentrating capacity in our patients with compulsive water drinking was not related to the quantity of water they consumed; for example, patient No. 2, who drank up to 20 litres a day, concentrated her urine normally with vasopressin. There did not appear to be any connexion between the ability to concentrate and the plasma osmolality. In the present state of knowledge it is even more difficult to understand why some patients with diabetes insipidus have an impaired ability to concentrate with vasopressin; this phenomenon has also been noted by Fradiss (1926), Biggart (1937), and Kleeman, Maxwell, and Witlin (1958). Biggart's (1937) evidence suggests that resistance to vasopressin in diabetes insipidus is due to a lesion of the nuclei in the tuber cinereum. The clinical importance of these findings is that, when a patient's ability to secrete ADH is being gauged by the changes in urine concentration which follow fluid deprivation, a correct interpretation is not possible unless the ability to concentrate with vasopressin is already known.

In normal subjects the urine concentration is slightly greater after fluid deprivation than after the administration of a saturating dose of vasopressin (Jones and de Wardener, 1956). Accordingly it has been proposed above that, if the urine concentration with fluid deprivation is greater than after vasopressin, it can be assumed that the ability to secrete ADH is normal; but that if the urine concentration with fluid deprivation is less than after vasopressin, the ability to secrete ADH is below normal; these assumptions are valid only if the outputs of solute are similar during fluid deprivation and after vasopressin. On this basis six of the eight patients with compulsive water drinking were able to secrete ADH normally, whereas the other two, and all the patients with diabetes insipidus, had an impaired ability to secrete ADH. The abnormal response of these two cases of compulsive water drinking to vasopressin tannate, however, and their subsequent ability after treatment to concentrate normally with fluid deprivation, showed that they were not suffering from diabetes insipidus (that is, a persistent defect in the ability to secrete ADH) but had a transient inhibition of ADH secretion. A brief emotional diuresis, due to an inhibition of ADH secretion during a fluid deprivation test, has been described

previously in normal subjects and in patients with hypertension (Miles and de Wardener, 1953). The striking feature in the two patients with compulsive water drinking (Nos. 1 and 2) was that the phenomenon persisted throughout the period of fluid deprivation; in patient No. 2 this had previously led to a confident diagnosis of diabetes insipidus.

Other workers have tested the integrity of the neurohypophyseal system by observing the response of the urine flow to intravenous nicotine (Cates and Garrod, 1951; Lewis and Chalmers, 1951; Dingman, Benirschke, and Thorn, 1957) or hypertonic saline (Gilman and Goodman, 1937; Hare, Hare, and Phillips, 1943; Hickey and Hare, 1944; Carter and Robbins, 1947; Cates and Garrod, 1951). Nicotine stimulates a release of ADH by a direct effect on hypothalamic nuclei (Burn, Truelove, and Burn, 1945), whereas a hypertonic solution raises the plasma osmolality, which in turn stimulates osmoreceptors to initiate the release of ADH (Verney, 1946). It is doubtful whether in man nicotine has any effect on the neurohypophysis unless the amount given is sufficient to cause sweating, nausea, and vomiting. Dingman, Benirschke, and Thorn (1957) have recorded three patients with compulsive water drinking in whom nicotine failed to produce a change in urine flow, though the flow diminished with hypertonic saline. In differentiating compulsive water drinking from diabetes insipidus, therefore, nicotine appears to be both unpleasant and unreliable. Published reports are almost unanimous that hypertonic saline is more reliable, and in nine out of the 10 recorded cases of compulsive water drinking it produced a decrease in urine flow; but in the remaining patient there was an increase in salt excretion and urine flow, and the response was therefore the same as that obtained in diabetes insipidus. Similarly, in two of our compulsive water drinkers this test produced a misleading increase of solute output and urine flow, and it was not used again. It is evident that tests of neurohypophyseal function, including fluid deprivation, may sometimes show that a patient with compulsive water drinking has an impaired ability to secrete ADH. An inability to secrete ADH with one test alone, therefore, should not be taken as conclusive evidence that the patient suffers from diabetes insipidus. In addition to their occasional unreliability, all these tests have other disadvantages. Those associated with nicotine have been mentioned. Hypertonic saline may precipitate pulmonary oedema and cardiac failure (White, 1954) or an osmotic diuresis which obscures the interpretation of the test, whether or not there has been a release of ADH. Fluid deprivation may be an arduous procedure for a patient with polydipsia, and it may cause severe side-effects if it is not properly controlled. Alternatively, surreptitious drinking may invalidate the result. If the test is explained thoroughly beforehand, however, and is stopped when 3 to 5 per cent. of the body weight has been lost or after 24 hours, whichever is the sooner, most patients with compulsive water drinking or diabetes insipidus will withstand the ordeal with fortitude. The weight should be measured frequently, sometimes at hourly intervals; in this way not only can excessive loss be prevented, but a continued intake of fluid can be detected, for a brisk urine flow will then persist without a change in weight.

The effect of a long-acting vasopressin preparation was a useful diagnostic feature in two of our patients (Nos. 1 and 2) with compulsive water drinking. Fluid deprivation suggested that they were suffering from diabetes insipidus, but with vasopressin tannate in oil one developed acute overhydration, and the other felt ill, and her headache and hypertension became more severe. The failure of vasopressin tannate to cure the thirst of compulsive water drinkers, in contrast to its effect in diabetes insipidus, has been noted before (Gardiner-Hill, personal communication), and the sudden onset of severe overhydration with vomiting after its administration has been reported by Cates and Garrod (1951). In compulsive water drinking vasopressin tannate reduces the urine flow, however poor the kidney's ability to concentrate; and subsequently the fluid intake decreases, presumably because of the nausea and discomfort of over-hydration. Superficially, therefore, the response to vasopressin tannate may be the same as in diabetes insipidus; the important clinical distinction is that in compulsive water drinking vasopressin tannate makes the patients feel ill, whereas in diabetes insipidus it makes them feel better.

It was difficult to influence the fluid intake in compulsive water drinking. Some patients could be persuaded to drink less by direct suggestion, but they usually found this increasingly difficult, and soon reverted to their former state. Electroconvulsive therapy and continuous narcosis also produced only temporary remissions, except in patient No. 2 (aged 57), in whom improvement for two years followed a period of continuous narcosis. Nevertheless, as compulsive water drinking has not been reported after the age of 60, it is possible that the condition terminates naturally at about that time.

In conclusion, a diagnosis of compulsive water drinking is probable if, in the absence of renal disease or glycosuria, polydipsia and polyuria are intermittent, or if they are associated with other gross psychological disturbances, or if definite evidence of ADH secretion can be obtained. Alternatively, a diagnosis of diabetes insipidus is probable if, in addition to evidence of inability to secrete antidiuretic hormone, there are signs of a lesion in the neighbourhood of the neurohypophysis, for example, a calcified suprasellar cyst or a visual-field defect. The distinction between compulsive water drinking and diabetes insipidus is difficult in the presence of the following features: (1) persistent polydipsia and polyuria; (2) a normal mental state on superficial observation; and (3) when a test of neurohypophyseal integrity suggests that the ability to secrete antidiuretic hormone is impaired, but there are no other signs of a lesion in the region of the neurohypophysis. In these circumstances the ability to secrete antidiuretic hormone should be investigated by another test, for if a normal response to a test of neurohypophyseal integrity can be obtained by any means the diagnosis of diabetes insipidus is excluded. If it cannot be obtained, a diagnosis of diabetes insipidus is probable unless the plasma osmolality is below 275 m-osmoles per kg., or detailed observation and inquiry point to a definite psychological disorder, or treatment with vasopressin tannate in oil makes the patient ill.

APPENDIX

Case 2. A married woman aged 57 was admitted on December 1, 1956 for investigation of polydipsia and polyuria. She was one of 13 siblings, and had a happy and healthy childhood. Neurotic tendencies were sleep walking, over-conscientiousness, and impulsiveness. She did well at school, especially at mathematics; she left at 16, and worked in a bank until she was 21. At 17 she ran away from home because her drunken father was beating up the family; she married at 18, and had a son at 25 and a miscarriage at 32. One of her sisters developed asthma at the menopause. Between the ages of 33 and 37 she had her left ovary, a pelvic tumour, and a 'growth in the front passage' removed; she also had an operation for repair of a left ptosis. At 43 an orthopaedic surgeon considered that she was suffering from 'summer oedema'. At 44 she was investigated for abdominal pain, but no cause was found. At 46 (February 1945) she had a submucous myomectomy, and when in the ward was found to be drinking water excessively. A psychiatrist's report included the statement that 'Mrs. — is obviously a woman who has been pestered by all sorts of deep-seated emotional difficulties for years and years. She has managed to achieve a very fair degree of success'. At 48 she was admitted to yet another hospital because of persistent polydipsia and polyuria. The history at this time was that her symptoms had started after a bomb incident, and that she had had a remission after the alleged death of her son. During her stay in hospital she had several 'attacks of paralysis', which were considered to be functional. On several occasions she was discovered to be pouring water into the bed-pan. She was considered to be suffering from hysterical polydipsia. At 49 (November 1948) she had a vaginal hysterectomy for menopausal menorrhagia and vaginal prolapse. This was followed by parametritis, thrombophlebitis, a brain-stem thrombosis, and hysteria. Two months later she had recovered from the cerebral lesion, and residual symptoms were attributed to anxiety and hysteria. From the age of 50 to 55 the progress of her polydipsia and polyuria is uncertain, but she then had a sudden exacerbation, and began to drink up to 17 litres a day. At 55 she had had shortness of breath on exertion for five years, and feelings of suffocation, with hot flushes, for three years. She was admitted to a mental hospital and given deep narcosis, but this had no effect on the drinking. She was then admitted to a general hospital for re-investigation of the polydipsia and polyuria. It was found that her urine output was about 15 litres a day, that she failed 'to concentrate her urine' after fluid deprivation, or the administration of nicotine, but that there was a 'good response' to vasopressin tannate in oil. Air encephalogram, sugar tolerance, serum calcium, plasma phosphorus, and urinary ketosteroid excretion were normal. She was considered to have diabetes insipidus, and treated with vasopressin tannate in oil, but it made her feel bloated and ill, and after a few months she gave up the injections.

A year later, at the age of 56, she became depressed and returned to a mental hospital for four months. She now felt ashamed, and thought she was going mad. She isolated herself, and did not wash. Her mouth felt 'dammed up', her taste, smell, and sight were impaired, and 'everything seemed dark'. Though she complained that her appetite had been 'destroyed', her weight increased. She was again given vasopressin tannate in oil, and was discharged unimproved. Her thirst was now so severe that on one occasion she drank the water from a vase of flowers; eventually she moved into the bathroom, with a mattress, to be near the tap and the lavatory. Two months later she was admitted.

On examination she was a florid, plump woman, with thick red hair; she looked younger than her age, and spoke in a histrionic manner. She was co-operative

in giving her history, but was easily agitated and upset. She had ptosis of the left eyelid which fluctuated in intensity. There was slight oedema of the ankles and sacrum, and slight weakness of the right arm and leg. Her blood-pressure was 150/90. Plasma-electrolyte concentrations were: sodium 127 m-equiv., potassium 3·7 m-equiv., chloride 91 m-equiv., and bicarbonate 25 m-equiv. per litre. The blood urea was 22 mg. per 100 ml., and the plasma osmolality 265 m-osmoles per kg.

During the first 10 days of her stay in hospital her urine output varied between 12 and 20 litres. The amount passed during the night was about half that passed during the day. The urine did not contain protein. A 24-hour creatinine clearance was 78 ml. per minute, and an intravenous pyelogram showed no abnormality. The highest urine concentration obtained with vasopressin was 734 m-osmoles per kg., and after fluid deprivation 113 m.-osmoles per kg.; but the administration of aqueous vasopressin at the end of the period of fluid deprivation raised the osmolality to 807 m-osmoles per kg. After the administration of five units of vasopressin tannate in oil the patient continued to drink excessively for seven hours; she became pale, bloated, inconsequential, giddy, and nauseated. She then vomited copiously for four hours, and developed a hysterical fugue, in which she was incontinent and immobile, refused to answer questions, and appeared unconscious. She remained in this state for 36 hours, and recovered after being given one litre of 3 per cent. sodium chloride intravenously (Fig. 6). On recovery she was alert and calm; for three weeks she had retrograde amnesia for the previous 10 days. She was less thirsty, and for the next few days managed to control her daily water intake to between 1·5 and 3·7 litres; but she found this increasingly difficult, her ptosis became more marked, and she easily showed panic if water was not immediately available. She was then advised to drink to satisfaction, and her fluid intake rose to about eight litres in 24 hours; three hours later the ptosis improved.

Subsequent progress and treatment. After a month the polydipsia and polyuria were unchanged. She was then treated with continuous narcosis for two weeks (Fig. 7); she improved considerably, and after fluid deprivation for 12 hours the osmolality of the urine was 832 m-osmoles per kg. Her thirst disappeared, but five weeks after discharge from hospital she developed hysterical weakness of the legs.

Summary. A woman of 57, with severe, chronic hysteria and an 11-year history of intermittent compulsive water drinking, who had had a recent admission to a mental hospital for depression. Her ability to concentrate the urine was normal, but fluid deprivation revealed an impaired ability to secrete ADH; vasopressin tannate in oil made her ill. After treatment with continuous narcosis her fluid intake, and the ability to secrete ADH after fluid deprivation, returned to normal. There has been no recurrence of compulsive water drinking for two years.

Case 4. A single man aged 56. Thirst and polyuria developed in 1953, when he was 53. The patient's father was said to have had diabetes insipidus, and to have died of kidney trouble; an aunt was a dipsomaniac. He had had a public school and professional army officer's education, and was in the Army until the age of 23. He then worked as a planter in India and Ceylon until the age of 53, except during the war, when he was in the Army. At the ages of 25, 35, and 37 he had gonorrhoea. From 51 to 53 he developed a mild addiction to morphia because of sleeplessness and worries in connexion with his work, and during this time he lost much weight. The only morphia available was in ampoules com-

bined with atropine, and his excessive thirst started at this time. He developed symptoms from a papilloma of the bladder when he was 53, and returned to England. He was treated by fulguration 18 times in the next three years, and during this period he complained that his 'mucous membranes had gone wrong', that his mouth was perpetually dry, and that he ached 'everywhere'. He also complained of difficulty in swallowing, and that food stuck at the level of the upper border of his sternum. He stated that he was sleepless, constipated, and flatulent, and unable to empty his bladder properly. By March 1956 he had lost about 29 kg. in weight, and his blood-pressure had risen from 165/80 to 220/120. Intravenous and retrograde pyelograms, indirect laryngoscopy, and barium swallow were all normal. It was considered that his difficulty in swallowing was 'functional'. He was first noticed to have excessive thirst and polyuria in December 1954. On 27.5.56 he had a typical attack of grand mal; no abnormal neurological signs were found, and he was transferred for further investigation.

On examination he was a bearded, emaciated, and psychotically depressed man. He was co-operative, but severely retarded. He spoke in a slow, slurred, and barely audible voice. His mood was one of utter hopelessness, and he was totally preoccupied with the delusion that he was completely dried up, and that his intestines and urinary system were blocked. He attributed this to the morphine addiction three years previously. The fundi were normal, and the blood-pressure 205/110. Chest and skull X-rays and a barium swallow were normal. An electroencephalogram taken soon after the grand mal attack showed no specific abnormality. Wassermann and Kahn tests were negative. Plasma-electrolyte concentrations were: sodium 139 m-equiv., potassium 4·7 m-equiv., chloride 96 m-equiv., and bicarbonate 31 m-equiv. per litre. The blood urea was 18 mg. per 100 mg., and the plasma osmolality 263 m-osmoles per kg. The total exchangeable sodium was 59·5 m-equiv. per kg. (normal in this laboratory 39 to 48 m-equiv. per kg.). The urine volume varied between 5·6 and 12 litres per day; usually the amount passed during the night was about half that passed during the day. The urine contained a trace of protein. A 24-hour creatinine clearance was 78 ml. per minute. The highest urine osmolality obtained with vasopressin was 289 m-osmoles per kg., and after fluid deprivation 505 m-osmoles per kg.

Subsequent progress and treatment. Treatment of the depression with electroconvulsive therapy was started on 22.6.56. There was a rapid improvement in the thirst, and the effect on the polyuria is shown in Fig. 7. There was a dramatic change in the patient's mental state; he now smiled and laughed, and made himself useful in the ward. Appetite returned, and in the next two months he gained 13 kg. in weight. His blood-pressure fell to 180/85. Six months later many of the symptoms, including thirst, had returned, but were less severe.

Summary. A man of 56, with a psychotic depression and fluctuating hypertension, who developed compulsive water drinking when addicted to morphia and atropine at the age of 53. The ability to concentrate the urine was severely impaired; fluid deprivation showed a normal ability to secrete ADH. His mental state, the compulsive water drinking, and the blood-pressure, improved with electroconvulsive therapy, but there was some relapse after six months.

Case 7. A married woman, aged 51, was admitted on November 6, 1957, complaining of polydipsia and polyuria for seven months. She came from a healthy family. When she was three years old her mother died in childbirth. As a child

she walked in her sleep. Her father married again, and she was kept away from school a great deal to look after her step-brothers and sisters. She lacked learning, but was not mentally defective. She had a stable, if brief, work history until she married at 19. The menarche was at 17, and menstruation was normal until she was 36. The menopause was at 45, and since then she suffered from hot flushes, giddy spells, and headaches. Between the ages of 25 and 40 she had five children; a son, aged 26, and two daughters, aged 19 and 11, survived. At the ages of 36 and 41 she had two episodes of amenorrhoea, one lasting nine months; she was convinced she was pregnant on each occasion. Her married life had been satisfactory until her husband made a girl pregnant and had to pay maintenance. Three years previously her son left home temporarily after trouble with the police. He was a constant worry to the patient, but helped her to look after his 19-year-old sister's illegitimate baby. This daughter had gone off with a man aged 32, who was not the father of the child, and whom the patient regarded as unsuitable. She thought he was too old, and a 'spiv'. Finally, in April 1957, this recalcitrant daughter walked out in a huff, married the 'spiv', and left the patient literally holding the baby. To add insult to injury, the patient was excluded from the wedding arrangements. The polydipsia and polyuria started at this time.

She had put on much weight after the birth of her fourth child at the age of 32, and again at the menopause. In the next two years she had an operation for prolapse, and a Mayo repair of a large para-umbilical hernia; recovery from the latter was complicated by thrombophlebitis and a pulmonary embolism. Pain and urgency of micturition occurred both before and after the operation for prolapse, but no physical cause could be found. In January 1952, at the age of 46, she had a further laparotomy because of pain at the site of the hernia operation, and a piece of steel wire was removed. In the next five years she had intermittent abdominal pain, for which no cause could be found. Two cholecystograms were normal; one of these caused a prompt relief of pain. In April 1957, at the culmination of her domestic crises, she started to wear an abdominal belt, which she considered to be the cause of her polyuria and incontinence. She also complained of sleeplessness, feeling at her worst in the morning, and that she 'couldn't be bothered'.

On examination she was a co-operative but poor historian, and reproached herself for the behaviour of her family. She was a very obese woman, with intertrigo. Her weight was 108 kg., and height 152 cm. There was no evidence of prolapse or incontinence on straining, and appearances on cystoscopy were normal. Her blood-pressure was 138/80. X-rays of the skull were normal. Plasma electrolytes were: sodium 136 m-equiv., potassium 4·3 m-equiv., chloride 92 m-equiv., and bicarbonate 25 m-equiv. per litre; the plasma osmolality was 272 m-osmoles per kg. The blood urea was 21 mg. per 100 ml. Her daily urine output in the ward varied between 5·1 and 7·4 litres; there was no protein or glucose in the urine. A 24-hour creatinine clearance was 188 ml. per minute. The highest urine osmolality obtained with vasopressin was 602 m-osmoles per kg., and after fluid deprivation 850 m-osmoles per kg.

Subsequent progress. Six days after admission she had one of her attacks of abdominal pain and vomiting for a few hours. Thereafter the daily urine output was about two litres. She was discharged 10 days later. Polydipsia and polyuria have not recurred.

Summary. An obese woman of 51, with a florid history of social, domestic, and marital strife; she had had many operations and hysterical episodes, including several attacks of abdominal pains, and pseudocyesis twice. Compulsive

water drinking started at the peak of her domestic upheavals. Fluid deprivation and vasopressin tests showed that the ability to concentrate the urine and to secrete ADH were normal. Compulsive water drinking remitted spontaneously after an attack of abdominal pain and vomiting, six days after her admission, and has not recurred.

We would like to thank Dr. J. S. Staffurth for the estimation of exchangeable sodium, and Drs. J. St. C. Elkington, Evan Jones, H. Gardiner-Hill, B. Pollak, V. Wynn, and Mr. T. W. Mimpriss for their kindness in referring patients to us.

Summary

1. Seven women and two men with compulsive water drinking are described; their ages ranged from 48 to 59 years, except for one patient aged 24.

2. There was a history of previous psychological disorder in eight of the nine patients, including hysteria, delusional hypochondriasis, and depression; the observed psychological disturbances ranged from delusions, depression, and agitation, to frank hysterical behaviour; one patient appeared normal.

3. The consumption of water fluctuated irregularly from hour to hour or from day to day; in some patients there were remissions and relapses lasting several months or longer.

4. The mean plasma osmolality in eight compulsive water drinkers was significantly lower than normal; in 12 patients with diabetes insipidus it was significantly higher.

5. The ability to concentrate the urine after intravenous vasopressin varied considerably, and in some patients it was severely impaired; this defect was unrelated to the urine output (5 to 20 litres in 24 hours) or the plasma osmolality.

6. The urine concentration after fluid deprivation suggested that six patients were able to secrete ADH normally, but that in two the ability to secrete ADH was impaired. After a remission of the compulsive water drinking these two patients had a normal response to fluid deprivation.

7. Vasopressin tannate in oil made most patients feel ill; in one it caused acute over-hydration.

8. In four patients the fluid intake returned to normal after electroconvulsive therapy or a period of continuous narcosis; the improvement in three was transient, but in the fourth it has lasted two years.

9. Compulsive water drinking was distinguished from diabetes insipidus by the clinical history and mental state of the patient, and by a fluid deprivation test performed after the kidney's ability to respond to administered vasopressin had been established; an estimation of plasma osmolality, and the general effects produced by an injection of vasopressin tannate in oil, were also found useful.

REFERENCES

Biggart, J. H. (1937) *J. Path. Bact.* **44**, 305.
Burn, J. H., Truelove, L. H., and Burn, I. (1945) *Brit. med. J.* **1**, 403.
Carter, A. C., and Robbins, J. (1947) *J. clin. Endocr.* **7**, 753.
Cates, J. E., and Garrod, O. (1951) *Clin. Sci.* **10**, 145.
Dingman, J. F., Benirschke, K., and Thorn, G. W. (1957) *Amer. J. Med.* **23**, 226.
Epstein, F. H., Kleeman, C. R., and Hendrikx, A. (1957) *J. clin. Invest.* **36**, 629.
Fradiss, L. (1926) *Le Diabète insipide*. Paris.
Gilman, A., and Goodman, L. (1937) *J. Physiol.* (*Lond.*) **90**, 113.
Hare, R. S., Hare, K., and Phillips, D. M. (1943) *Amer. J. Physiol.* **140**, 334.
Hickey, R. C., and Hare, K. (1944) *J. clin. Invest.* **23**, 768.
Jones, R. V. H., and de Wardener, H. E. (1956) *Brit. med. J.* **1**, 271.
Kleeman, C. R., Maxwell, N. H., and Witlin, S. (1958) *A.M.A. Arch. intern. Med.* **101**, 1023.
Lewis, A. A. G., and Chalmers, T. M. (1951) *Clin. Sci.* **10**, 137.
Miles, B. E., and de Wardener, H. E. (1953) *Lancet*, **2**, 539.
Verney, E. B. (1946) Ibid. **2**, 739.
de Wardener, H. E., and del Greco, F. (1955) *Clin. Sci.* **14**, 715.
—— and Herxheimer, A. (1957) *J. Physiol.* (*Lond.*) **139**, 42.
White, A. G. (1954) *New Engl. J. Med.* **250**, 633.

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THE EXCRETION OF ACID IN RENAL DISEASE[1]

BY OLIVER WRONG AND H. E. F. DAVIES

(From the University Department of Medicine, Manchester Royal Infirmary, and the Medical Unit, Cardiff Royal Infirmary)

With Plates 19 and 20

IN normal circumstances the metabolism of the body produces an excess of non-volatile acid over base, and a systemic acidosis would result were it not for the ability of the kidney to excrete urine more acid than body fluids and appreciable quantities of ammonium. Excretion of acid is impaired in renal disease, and acidosis frequently results; yet there is little information as to how the chief variables of acid-excretion are affected in different forms of renal disease. The main purpose of the present work was to devise a short test for the detection of patients with impaired excretion of acid. The function of eliminating acid has usually been assessed by measuring the renal response to an acidifying stimulus such as hydrochloric acid or ammonium chloride. The only detailed studies reported using this technique have lasted five or more days (Begun and Munster, 1919; Linder, 1927; Salvesen, 1928; Albright, Burnett, Parson, Reifenstein, and Roos, 1946) and, although valuable information has been gained, such a procedure is clearly too time-consuming for routine use. Lundbaek (1951) and Rosenheim (1956) have described a shorter test, based on the same principle and lasting only a few hours, but they each reported results on only one patient, and the general significance of their findings is therefore open to question. We have used a similar short test on a large number of normal subjects and patients with various forms of renal disease. Our results, some of which have already been published in summarized form (Davies and Wrong, 1957), indicate that this test gives a reliable criterion of the ability to excrete acid. Certain other points which arose in the course of the study have also been investigated.

Physiological Considerations

Acids owe their acidic properties to the presence of hydrogen ions, and hence it is the excretion of hydrogen ion that primarily concerns the present paper; excretion of acid-radicals, or anions, poses different problems, and will receive little attention here. The distinction between *acids* (which give up hydrogen ion) and *anions* (electronegatively charged ions) is important, and Relman (1954) and Christensen (1957) have pointed out the confusion which has arisen because the terms are often used interchangeably. An example of this confusion

[1] Received June 19, 1958.

[2] Now at the Medical Unit, University College Hospital, London.

is the frequently made statement that renal acidosis 'arises from retention of fixed anion within the body'. Acidosis, an increase in the hydrogen-ion concentration of body fluids, can result only from retention of hydrogen ion or loss of hydroxyl ion; retention of anions such as phosphate, sulphate, or chloride cannot cause acidosis, although the two abnormalities frequently coexist. A reduced plasma concentration of bicarbonate, however, in the presence of normal respiratory function, is customarily regarded as evidence of an extracellular acidosis (Van Slyke and Cullen, 1917), for an increase in hydrogen-ion concentration in the plasma directly reduces the concentration of bicarbonate ($H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$).

A normal person excretes 40 to 80 m-equiv. of hydrogen ion daily through the kidneys. This hydrogen ion arises mainly from the oxidation of sulphur and phosphorus contained in dietary protein to sulphuric and phosphoric acids; Hunt (1956) has shown that sulphur is quantitatively the more important of the two. These mineral acids do not account for all the hydrogen ion excreted, and there is a small component of presumably organic origin. The kidneys can excrete urine as acid as pH 4·5, or 800 times the hydrogen-ion concentration of plasma (Pitts, Lotspeich, Schiess, and Ayer, 1948), but even at this low pH the urine contains negligible amounts of free hydrogen ion—about 0·03 m-equiv. per litre. Apart from this minute amount, all the hydrogen ion excreted by the kidneys is combined, either with urinary buffers as *titratable acid* or with ammonia as *ammonium*.

Titratable acid. Hydrogen ion which is combined with buffer can be estimated by titrating urine with alkali to pH 7·4, the pH of plasma. The greater part is combined with phosphate buffer, but in addition urine contains a number of organic buffers, one of which is creatinine. It is now generally agreed, mainly as a result of the work of Pitts and his colleagues (summarized by Pitts, 1953), that excretion of titratable acid is accomplished by renal tubular secretion of hydrogen ion. Transfer of hydrogen ion from tubular cell to urine is probably effected in exchange for sodium ions passing in the opposite direction (Berliner, 1952). A plentiful supply of hydrogen ion is available in the tubular cell from the hydration of carbon dioxide to carbonic acid, a reaction catalysed by carbonic anhydrase, and the dissociation of this acid to bicarbonate and hydrogen ions. The chief factors limiting the rate of excretion of titratable acid are the minimum urinary pH which the kidneys can achieve, and the rate of excretion of buffer. For when acidotic subjects are made to excrete more buffer than usual (by intravenous infusion of phosphate) their excretion of titratable acid increases in proportion, and urinary pH remains low. By this means Pitts, Lotspeich, Schiess, and Ayer (1948) obtained rates of excretion of titratable acid equivalent to 500 m-equiv. daily, without any evidence of an intrinsic limit to the rate of hydrogen-ion secretion.

Ammonium. Urine contains variable amounts of ammonium, conveniently regarded as hydrogen ion bound to ammonia ($H^+ + NH_3 = NH_4^+$).* Rather

* By convention urinary ammonium is usually called ammonia. To us this usage seems undesirable, for it conceals the carriage of hydrogen ion which is involved.

more hydrogen ion is excreted in this way than as titratable acid. In the dog, and probably in man as well, urinary ammonium is formed by the breakdown of glutamine in the tubular cell, under the action of glutaminase, to ammonia and glutamic acid; the deamination of certain amino acids provides some additional ammonia (Van Slyke, Philips, Hamilton, Archibald, Futcher, and Hiller, 1943). Ammonia is highly diffusible, and is thought to move passively into the tubular urine, where it combines with hydrogen ion already present to form ammonium. The rate of this movement is probably determined by the concentration gradient of free ammonia across the cell membrane, and hence largely depends on the urinary hydrogen-ion concentration (Robinson, 1954; Orloff and Berliner, 1956). There are at least three possible variables which limit the rate of excretion of ammonium—availability of substrate, enzyme activity, and urinary pH. Normally the last factor is probably the most important, for Wolf (1947) and others have shown a close relationship between ammonium excretion and urinary pH. But the activity of renal glutaminase may also be a limiting factor, for Davies and Yudkin (1952) have shown in the rat that a chronic acidosis increases both renal glutaminase and the excretion of ammonium, and alkalosis has the opposite effects. In man a greater increase in the excretion of ammonium is known to result from a sustained than from an acute acidosis, even for the same depression of urinary pH (Gamble, Blackfan, and Hamilton, 1925), and this effect could be due to an increase in renal glutaminase.

Bicarbonate. Physiologically bicarbonate is a base, for it can give up hydroxyl ion ($HCO_3^- \rightarrow CO_2 + OH^-$) or accept hydrogen ion ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$). About 3,500 μ-equiv. per minute are normally filtered through the glomeruli, but all, or nearly all, of this large amount is reabsorbed by the renal tubules. The available evidence suggests that most of this bicarbonate is removed from the tubule by reaction with secreted hydrogen ion: hydrogen ion combines with bicarbonate to form carbonic acid, which dissociates, and the carbon dioxide liberated diffuses out of the tubule (Brazeau and Gilman, 1953; Dorman, Sullivan, and Pitts, 1954). It is not certain whether tubular reabsorption of bicarbonate as such also occurs.

It follows that probably all the hydrogen ion excreted in the urine, either as titratable acid or ammonium, is initially hydrogen ion secreted by the renal tubule, and that this process may also explain the disappearance of filtered bicarbonate. But the exact stimulus for hydrogen-ion secretion is still uncertain. Three groups of workers have shown that there is a close relationship between hydrogen-ion secretion and the partial pressure of carbon dioxide (pCO_2) in body fluids (Brazeau and Gilman, 1953; Relman, Etsten, and Schwartz, 1953; Dorman, Sullivan, and Pitts, 1954). The pCO_2 of body fluids is closely linked to intracellular pH, and, although the latter cannot be directly measured, it may be the variable which determines the rate of hydrogen-ion secretion (Roberts, Randall, Sanders, and Hood, 1955).

Acidosis in Renal Disease

Generalized renal failure. Since the observations of von Jaksch (1888) it has

been recognized that severe renal failure with uraemia is frequently complicated by a metabolic acidosis. The first detailed studies of acid-excretion in this condition were made by Henderson and Palmer (1915), who found a reduction in the excretion of ammonium, subsequently confirmed by Hartman and Darrow (1928) and by Salvesen (1928). Van Slyke, Linder, Hiller, Leiter, and McIntosh (1926) observed that this reduction was roughly proportional to the fall in urea clearance. There is less certainty about the excretion of titratable acid. Many modern authorities (for example, Fishberg, 1954; Rosenheim, 1956) have stated without reservation that the diseased kidney is unable to excrete urine of maximal acidity, but this is not in accord with the experience of earlier workers. Henderson and Palmer (1915) found that patients with 'chronic nephritis' (many of whom were clinically uraemic, and probably acidotic) excreted urine of higher titratable acidity and lower pH than did normal subjects, and their conclusions were supported by those of Van Slyke, Linder, Hiller, Leiter, and McIntosh (1926), who, although they did not record urinary pH, reported that in chronic nephritis 'the titratable acidity was relatively well maintained until the final stage of complete renal insufficiency'. The serum concentrations of phosphate and sulphate are usually raised in severe renal failure (Peters and Van Slyke, 1931). Increased serum phosphate may cause certain of the features of uraemia, such as hypocalcaemia and secondary hyperparathyroidism, but retention of these two anions alone cannot be held responsible for acidosis (Schwartz and Relman, 1957). High levels of these anions are, in fact, frequently found in the serum of patients with renal failure who have never had acidosis, or in those whose acidosis has been successfully treated with alkalis.

Renal tubular acidosis. In recent years acidosis has been encountered in a number of different forms of renal disease which are characterized by tubular abnormalities but little diminution in glomerular function. The commonest of these syndromes, variously known as 'renal tubular acidosis' or 'renal hyperchloraemic acidosis', was first described by Butler, Wilson, and Farber in 1936, and has been most extensively studied by Albright and his colleagues (Albright, Consolazio, Coombs, Sulkowitch, and Talbott, 1940; Albright, Burnett, Parson, Reifenstein, and Roos, 1946). According to Albright the fundamental defect is an inability of the renal tubule to elaborate a normally acid urine and ammonium. As a result the anions produced by metabolism are excreted in the urine accompanied by excessive amounts of sodium, potassium, and calcium, leading both to a systemic acidosis and deficiencies of these cations. The presenting symptoms and signs are usually those of osteomalacia or potassium deficiency, and the majority of patients have had nephrocalcinosis or renal calculi, attributed by Albright to increased excretion of calcium. Hyperchloraemia is the rule, and is usually thought to result from shrinkage of the extracellular space following loss of sodium. The syndrome is a well-defined clinical entity, and so far over 50 cases have been described.

A form of 'renal tubular acidosis' affecting infants is also recognized, but some important differences suggest that it is not exactly the same condition. Like the syndrome in adults and older children, it is characterized by a hyper-

chloraemic acidosis and the excretion of an alkaline or only slightly acid urine containing little ammonium (Butler, Wilson, and Farber, 1936; Lightwood, Payne, and Black, 1953). But nephrocalcinosis is less common, and hypokalaemia and rickets have only rarely been recorded; instead, the disease manifests itself with signs of dehydration, failure to gain weight, vomiting, and constipation. If such infants survive, they usually do not develop the adult form of the syndrome, and their ability to excrete an acid urine and ammonium becomes normal (Buchanan and Komrower, 1958).

The Fanconi syndrome. A number of more or less distinct diseases, some inherited and others acquired, but all characterized by an excessive aminoaciduria of renal origin, are usually grouped together under this term (Stanbury, 1957*b*). Renal glycosuria, osteomalacia or rickets, potassium depletion, and a systemic acidosis are other inconstant features of the syndrome, but nephrocalcinosis, so common in renal tubular acidosis, has not been recorded. The renal abnormalities giving rise to acidosis appear to differ from patient to patient (Kyle and Canary, 1956), but this aspect of the syndrome has received little attention.

The Present Investigation

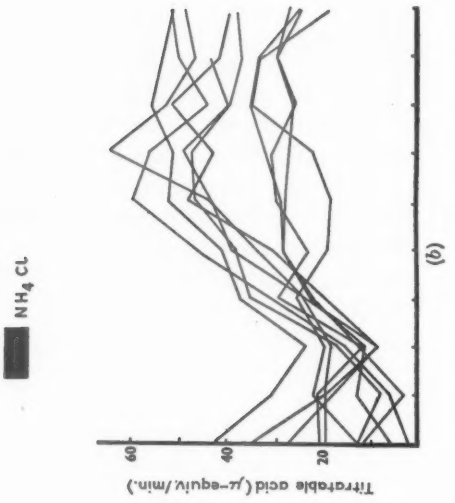
The subjects. Sixty-eight subjects have been studied. Table I shows how this large group has been subdivided; a few of the categories shown require further explanation. Under the heading *incomplete syndrome of renal tubular acidosis* are included three patients with generalized nephrocalcinosis; although none

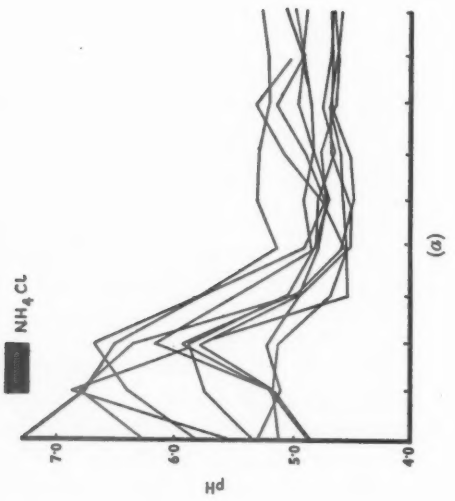
TABLE I

Subjects Studied

Diagnosis	*Number of subjects*
Normal renal function	10
General renal failure without evidence of tubular abnormality	16
Renal tubular acidosis	11
Incomplete syndrome of renal tubular acidosis	3
Unexplained generalized nephrocalcinosis	6
Bilateral renal calculi	4
Severe potassium depletion	3
Prolonged hypercalcaemia	10
Recovery from acute anuria	3
Adult Fanconi syndrome	2
Total	68

had a systemic acidosis, their response to ammonium chloride was similar to that of patients with renal tubular acidosis, and we therefore believe that they have an early or incomplete form of this syndrome. *Severe potassium depletion* is given as a separate diagnosis, regardless of the cause, as it is known that potassium depletion causes histological changes in the tubular epithelium (Relman and Schwartz, 1956) and interferes with the excretion of hydrogen ion (Clarke, Evans, MacIntyre, and Milne, 1955). Patients with *prolonged hypercalcaemia* are also grouped together. Hypercalcaemia of any origin may cause general renal failure; there is also evidence that it can selectively damage the


Titratable acid (μ-equiv./min.)
60
40
20
(b)
NH_4Cl


pH
7·0
6·0
5·0
4·0
(a)
NH_4Cl

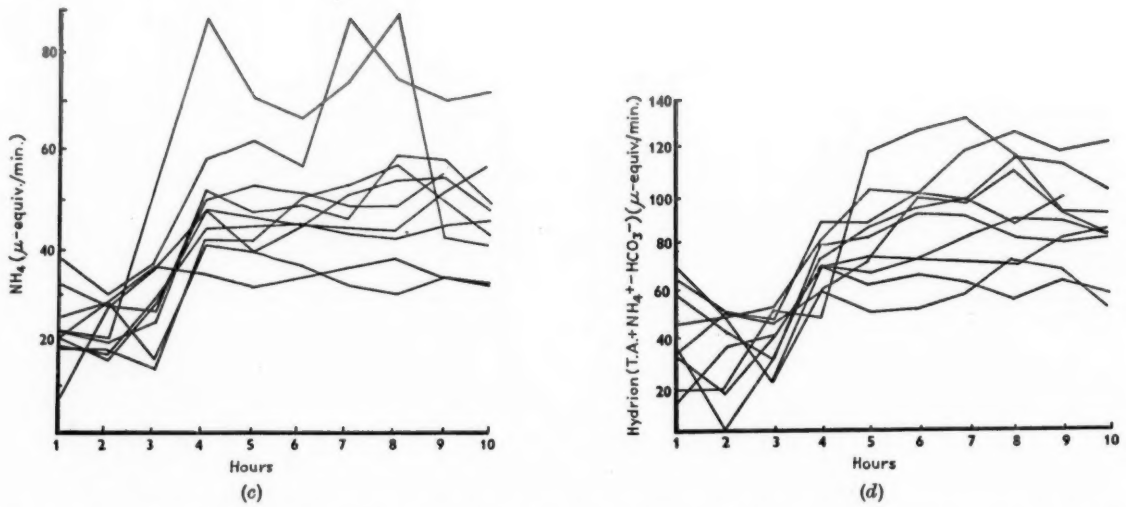


FIG. 1. Normal renal function: urinary pH and rates of excretion of titratable acid, ammonium, and total hydrogen ion after administration of ammonium chloride.

In this and subsequent charts negative values of titratable acid and total hydrogen-ion excretion are represented as nought. Total excretion of hydrogen ion (T.A.$+NH_4^+-HCO_3^-$) in urine more alkaline than pH 6·0 was calculated by using (T.A.$-HCO_3^-$) as described in Appendix I.

TABLE II

Normal Renal Function

Subject	Age	Sex	Weight (kg.)	Endogenous creatinine clearance (ml./min.)	Urea clearance (% of normal)	Plasma total CO_2 (m-moles/l.)		Urine, 2–8 hours after NH_4Cl						
						Before NH_4Cl	After NH_4Cl	pH	Titratable acid (μ-equiv./min.)	Inorganic P (mg./min.)	% of titratable acid due to P	NH_4^+ (μ-equiv./min.)	Total H^+ (μ-equiv./min.)	Diagnosis
1	14	M	33	..	..	26·6	23·6	4.61	27	0·56	53	33	60	Osteogenesis imperfecta
2	29	M	82	137	117	..	..	4·87	51	1·11	55	51	102	Normal
3	29	M	74	92	..	..	..	4·92	49	1·19	61	75	124	,,
4	30	M	67	149	..	29·5	24·6	4·60	49	1·00	52	69	118	,,
5	30	M	66	..	..	30·4	26·6	4·96	42	0·98	59	51	93	,,
6	30	F	61	..	..	30·6	26·0	4·72	42	0·83	50	49	91	,,
7	51	F	76	81	85	29·1	22·6	4·69	24	0·69	73	39	63	,,
8	55	M	81	85	77	29·3	27·1	4·59	39	0·77	51	45	84	Cervical spondylosis
9	58	M	53	..	..	32·3	28·8	5·24	30	0·83	69	48	78	Convalescent from pneumonia
10	64	M	62	..	73	30·0	26·6	4·90	26	0·56	55	44	70	Convalescent from appendicectomy
							Range	4·60–5·24	24–51	0·56–1·19	50–73	33–75	60–124	

tubular mechanisms of acid-excretion, for the syndrome of renal tubular acidosis has been known to complicate a number of diseases of which hypercalcaemia is a feature—primary hyperparathyroidism (Butler, Wilson, and Farber, 1936; Pratt, Geren, and Neuhauser, 1947; Leaf, 1951), vitamin-D intoxication (Fanconi and de Chastonay, 1950; Galan, 1955), and idiopathic hypercalcaemia of infants (Lightwood, Payne, and Black, 1953; Stapleton, 1956).

No patient with a positive urinary culture was included in the series, because of the possibility that bacterial action might convert urinary urea to ammonia *in vivo*; patients with oedema or receiving a low-salt diet were not included, because enhanced renal conservation of sodium might alter the response to ammonium chloride (Schwartz, Jenson, and Relman, 1955).

The short test of urinary acidification. Most subjects were studied in bed in the medical wards, but out-patients and healthy laboratory personnel remained up and about; no restrictions were placed on activity, meals, or smoking. Each subject emptied the bladder at 8 a.m., and thereafter at each hour until 6 p.m., any intermediate specimens being added together to give hourly collections. Male subjects passed specimens directly into clean glass bottles, female subjects into large beakers or clean aluminium bed-pans; all vessels contained a layer of liquid paraffin, and either a few ml. of toluene or a few crystals of thymol. No patient was catheterized as part of the present study. At 10 a.m., after two control collections of urine, each subject took ammonium chloride by mouth, 0·1 g. (1·9 m-equiv.) per kg. of body weight. This dose, 7 g. in an individual of average size, was taken over an hour to avoid gastric irritation. The salt was given in gelatin capsules containing 0·5 g. or 1 g., a preparation which is easily swallowed by most subjects, and only once caused vomiting. Three subjects could not swallow these capsules, and took compressed tablets or a solution of ammonium chloride instead. 'Enteric-coated' tablets were not given, because their absorption is known to be uncertain. Usually two samples of venous blood were taken, one just before and one two to four hours after ingestion of ammonium chloride. Blood was drawn into oiled and heparinized syringes, and immediately centrifuged and separated under paraffin. The analytical procedure for urine and plasma, and the calculations used, are described in Appendix I. Administration of ammonium chloride was followed by well-marked plasma changes. The level of total plasma CO_2 (bicarbonate and dissolved carbon dioxide) fell by $4{\cdot}1 \pm 1{\cdot}5$ m-moles per litre, and that of plasma chloride rose by $3{\cdot}7 \pm 2{\cdot}1$ m-equiv. per litre (mean and standard deviation of 42 paired observations). Plasma pH, calculated from the simultaneous pCO_2 of alveolar air, fell by an average of 0·06 unit in three observations. These changes did not differ appreciably between the various groups of subjects.

Results

Subjects with normal renal function (Figs. 1 to 3; Table II). This group consisted of 10 subjects, aged 14 to 64 years, without evidence of renal or cardiovascular disease. Fig. 1 shows the behaviour of the four most important variables

of acid-excretion—urinary pH, and the rates of excretion of titratable acid, ammonium, and total 'hydrogen ion'. The last variable, 'hydrogen ion', is obtained by adding together the excretion rates of titratable acid and ammonium (that is, hydrogen ion in combined form) and subtracting that of bicarbonate (hydroxyl or 'negative' hydrogen ion); the resultant figure indicates the net renal excretion of hydrogen ion. (This is a much smaller quantity than the hydrogen ion presumed to be secreted by the renal tubule; a simple calculation shows that over 95 per cent. of the latter is expended in neutralizing filtered bicarbonate, and never appears in the urine.)

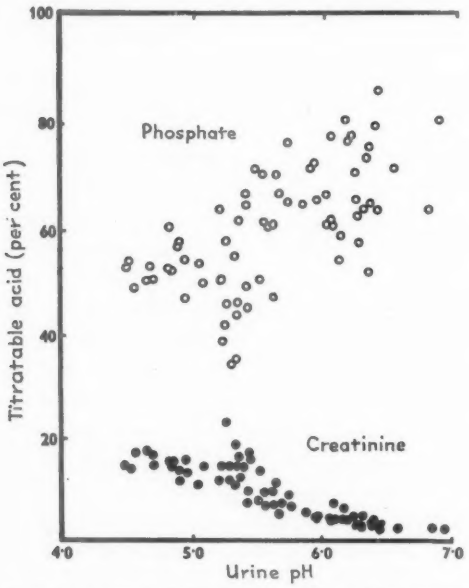


FIG. 2. Normal renal function: contributions of phosphate and creatinine to titratable acid.
Data from Subjects 4, 8, and 10.

Urinary changes following ammonium chloride were very rapid. All urine specimens passed more than two hours after its administration had a *pH* of 5·3 or less, and usually between 4·6 and 5·0, even when the plasma total CO_2 was still in the range usually regarded as normal (Table II). As the urinary pH does not fall lower than this after much larger doses of ammonium chloride (Pitts, Lotspeich, Schiess, and Ayer, 1948), we conclude that the dose used here is a stimulus to the healthy kidney to excrete maximally acid urine. Excretion of *titratable acid* rose rapidly as urinary pH fell, but continued to rise even after pH had become constant; calculation showed that this later increase could be entirely accounted for by increased phosphate excretion during the early afternoon, a normal feature of the diurnal excretory rhythm (Fiske, 1921). *Ammonium* excretion also increased sharply, and contributed rather more than

titratable acid to the total excretion of hydrogen ion. *Bicarbonate* was virtually absent from the highly acid urine specimens which followed ammonium chloride. The excretion of total *hydrogen ion* increased rapidly after administration of ammonium chloride, yet in the first eight hours the total excretion was equivalent to only 32 per cent. (mean figure) of the hydrogen ion derived from the ingested ammonium chloride. The total chloride excretion during the same time was, on the other hand, equivalent to 126 per cent. of that taken. All these urinary changes were fairly constant between two and eight hours after ingestion of ammonium chloride (periods 5 to 10). We have therefore averaged the results over this period (Table II), for comparison with corresponding figures from patients with renal disease.

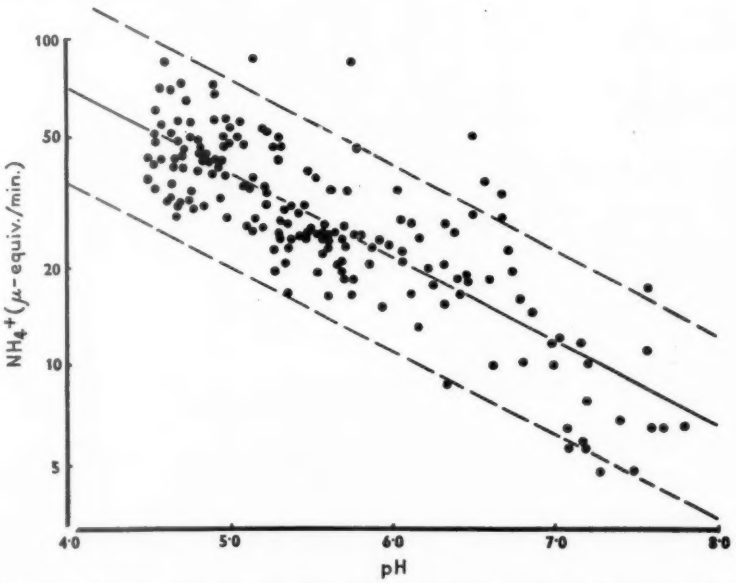
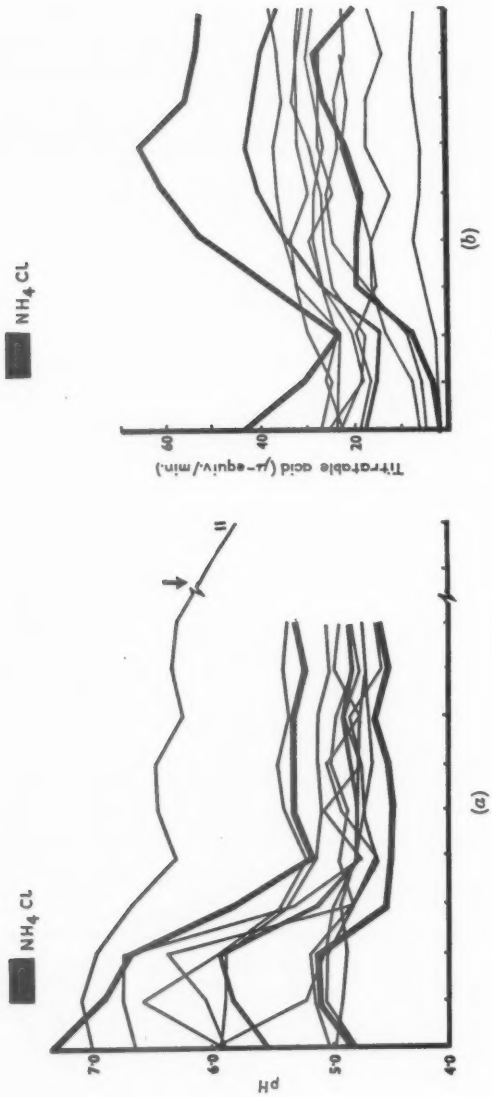


FIG. 3. Normal renal function: relationship between excretion of ammonium and urinary pH.

Data from all subjects; Subjects 2 and 3 also took small amounts of sodium and potassium bicarbonate to obtain alkaline urines. The calculated regression line and 95 per cent. range of observations are shown.

The titratable acidity of urine is often assumed to depend entirely on phosphate buffering. But we have calculated the contribution of phosphate to the titratable acidity of most of these specimens, and find that it is considerably less than 100 per cent. Some of these data are shown in Fig. 2. The proportion of titratable acid due to phosphate varied between 33 and 86 per cent. (mean 60 per cent.), being greatest when the pH of urine was close to the pK of phosphate, 6·85. Similar observations have been made by Milne (1956) and McCance and von Finck (1947). In the more acid urine collections creatinine (pK 4·97) contributed up to 20 per cent. of total titratable acid. About 30 per cent. of


NH4 Cl
(b)
Titratable acid (μ-equiv./min.)
60
40
20
NH4 Cl
(a)
pH
7.0
6.0
5.0
4.0

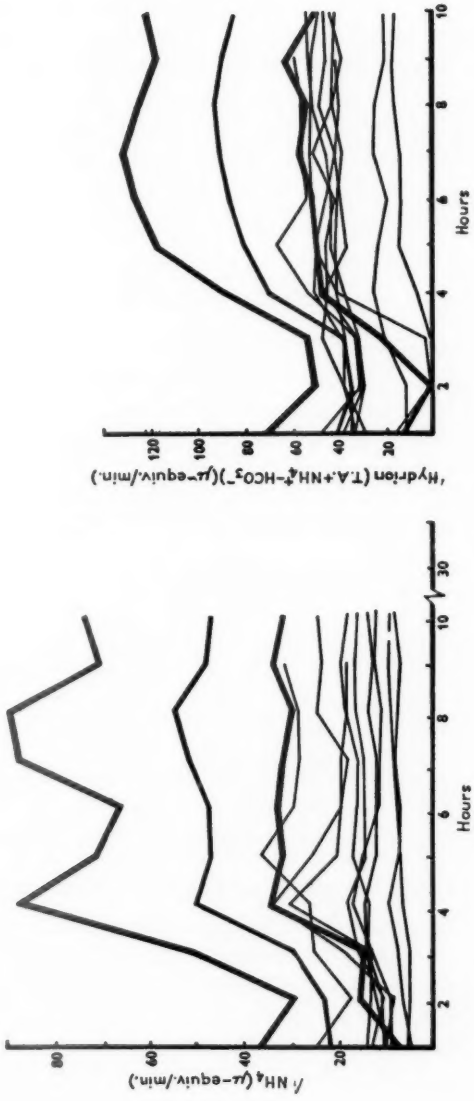


FIG. 4. General renal failure: excretion of acid after administration of ammonium chloride.
The mean and range of observations on normal subjects (Fig. 1) are shown by heavy lines. Subject 11 was given a second dose of ammonium chloride, as shown by the arrow.

titratable acid was not accounted for by these two buffers, and titration curves plotted for a number of these specimens suggested that the deficiency was not made up by any single buffer system. In acute experiments of this kind the excretion of ammonium bears a fairly constant relationship to urinary pH, the logarithm of the rate of excretion being a linear function of pH (Stanbury and Thomson, 1952; Clarke, Evans, MacIntyre, and Milne, 1955). Fig. 3 shows that this relationship held in the case of our normal subjects, the calculated regression line ($y = 2{\cdot}89 - 0{\cdot}259x$, where $y = \log NH_4^+$ (μ-equiv./min.) and $x = pH$) corresponding closely to that obtained by Clarke, Evans, MacIntyre, and Milne ($y = 3{\cdot}23 - 0{\cdot}3x$).

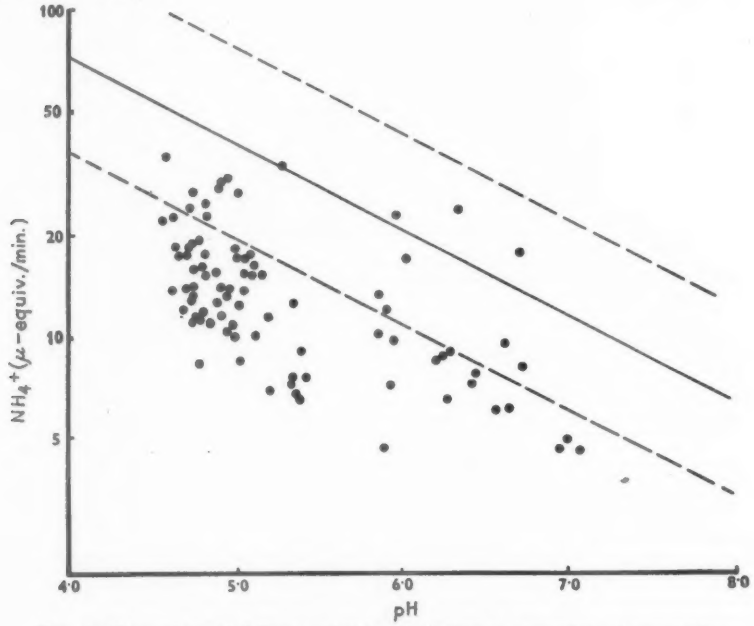


FIG. 5. General renal failure: relationship between excretion of ammonium and urinary pH.

The range of observations in normal subjects (Fig. 3) is also shown.

General renal failure (Figs. 4 and 5; Table III). Nine patients with disease of widely varying severity were given ammonium chloride; they were considered unlikely on clinical grounds to have specific tubular defects. Initially only one (Subject 14) had a definite acidosis (plasma total CO_2 20·7 m-moles per litre), although in several others the plasma total CO_2 concentration was in the lowest part of the normal range. Urinary changes were as rapid as in normal subjects. In most the *pH* fell to below 5·3, but in Subject 11 the pH fell only to 6·30 and, when further ammonium chloride was given on the following day, inducing a severe acidosis (plasma total CO_2 16·8 m-moles per litre), fell a little further to 5·90. It is of interest that this patient had a persistent and symptomless hypokalaemia, for mild potassium depletion may have been responsible for his

TABLE III

General Renal Failure

						Plasma, before NH_4Cl					*Urine, 2–8 hours after NH_4Cl*						
Subject	*Age*	*Sex*	*Weight (kg.)*	*Endogenous creatinine clearance (ml./min.)*	*Urea clearance (% of normal)*	*Urea (mg./100 ml.)*	*Total CO_2 (m-moles/l.)*	*Cl (m-equiv./l.)*	*K (m-equiv./l.)*	*Inorganic P (mg./100 ml.)*	*pH*	*Titratable acid (μ-equiv./min.)*	*Inorganic P (mg./min.)*	*% of titratable acid due to P*	*NH_4^+ (μ-equiv./min.)*	*Total H^+ (μ-equiv./min.)*	*Diagnosis*
11	19	M	31	7·3	10	70	22·5	102	3·0	4·2	6·33	6·3	0·22	63	7·6	10	Chronic pyelonephritis; osteodystrophy
12	24	M	52	11	14	91	25·0	98	4·0	5·7	5·35	14	0·40	71	6·9	21	Chronic glomerulonephritis
13	28	F	70	62	43	24	26·0	106	3·6	..	4·75	22	0·31	36	22	44	Recovery from acute glomerulonephritis
14	31	M	61	12	13	155	20·7	107	5·0	6·5	4·75	28	0·65	59	14	42	Chronic glomerulonephritis
15	35	M	71	33	34	64	27·9	99	3·9	4·2	4.75	36	0·77	54	15	51	Malignant hypertension
16	41	M	68	19	21	85	29·1	102	5·2	4·3	5·06	29	0·67	58	16	45	Malignant hypertension
17	53	M	69	28	18	100	23·2	103	5·0	..	4·92	32	0·66	52	12	44	Malignant hypertension
18	55	F	78	61 (inulin)	45	45	29·7	103	..	..	4·84	27	0·68	64	30	57	Gout; hypertension
19	64	F	72	41 (inulin)	26	42	22·2	106	4·3	..	4·70	20	0·40	51	19	39	Gout; chronic pyelonephritis; receiving salicylates
											Range	4·70–6·33	6–36	0·22–0·77	36–71	7–30	10–57

inability to excrete a more acid urine (see page 289). Excretion of phosphate buffer in the whole group was significantly reduced (0·53±0·20 mg. per minute as phosphorus, compared with 0·80±0·23 mg. per minute in normal subjects), resulting in a slightly reduced excretion of *titratable acid*, even in subjects who could excrete highly acid urine. Excretion of *ammonium* was more markedly impaired, and all patients were excreting less ammonium for their urinary pH than did subjects with normal renal function (Fig. 5). As a consequence of impaired excretion of both variables, the excretion of total *hydrogen ion* was invariably reduced.

TABLE IV

Advanced Renal Failure: Urinary pH of Patients with Uraemic Acidosis

Subject	*Age*	*Sex*	*Blood urea (mg./100 ml.)*	*Plasma total CO_2 (m-moles/l.)*	*Urinary pH*	*Diagnosis*
17	55	M	400	13·7	5·00	Malignant hypertension (2½ years after previous study)
20	19	M	300	16·7	6·15	Chronic glomerulo-nephritis
21	27	M	370	16·0	5·66	Subacute glomerulo-nephritis (Ellis type 1)
22	32	M	360	14·7	4·92	Malignant hypertension
23	35	M	260	15·0	5·21	Chronic glomerulo-nephritis
24	51	M	180	19·0	5·10	Collagen disease (? type)
25	51	F	250	8·0	5·28	Chronic glomerulo-nephritis
26	59	F	165	22·0	4·90	Malignant hypertension

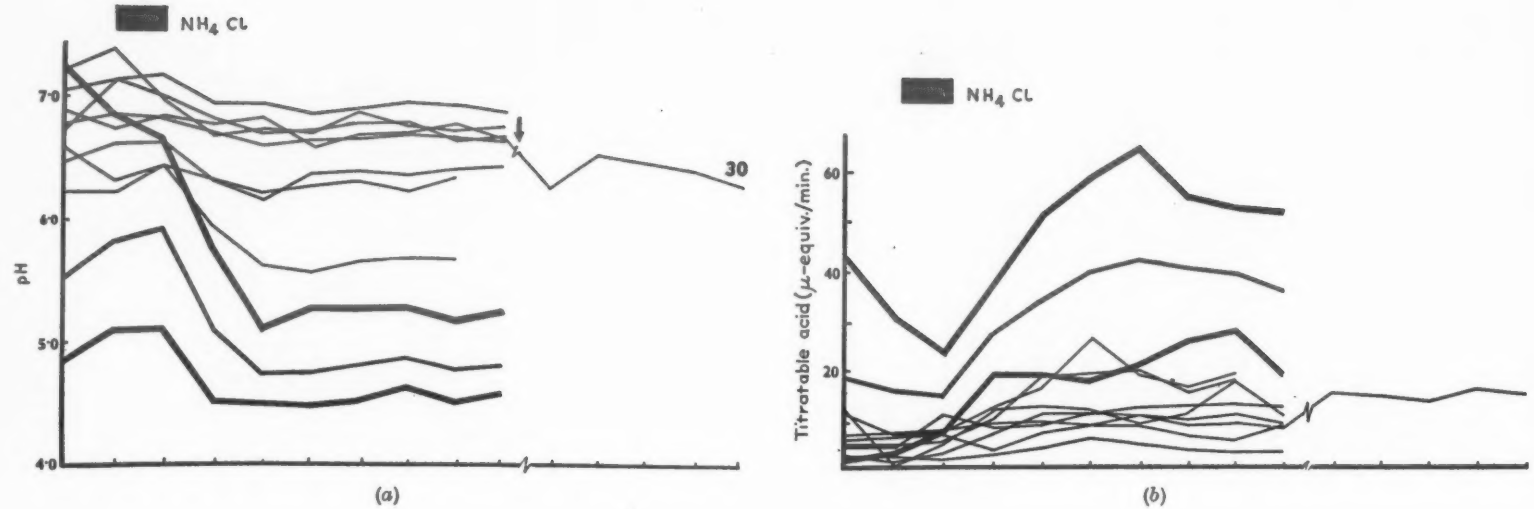
It is frequently stated that in renal failure the kidney is unable to form a normally acid urine. With one exception, our results did not support this conclusion. It seemed possible that the patients in the present group had not sufficiently severe renal failure to show this defect; accordingly we made a few observations on patients with extreme renal failure (Table IV). All these patients had a systemic acidosis, and it seemed neither justifiable nor necessary for our investigation to increase this by giving them ammonium chloride. A single random sample of urine was collected from each patient; in six cases out of eight its pH was under 5·3. We conclude that the ability of the kidneys to excrete an acid urine is not necessarily damaged in generalized renal disease, and usually remains unimpaired. Yet acidosis may develop as a result of, first, greatly reduced excretion of ammonium, and second, and to a lesser extent, reduced excretion of buffer and so reduced excretion of titratable acid.

Renal tubular acidosis. Eleven patients with this syndrome were studied; detailed case reports are given in Appendix II. All had initially presented symptoms due to renal calculi, osteomalacia, or potassium depletion, and all were found to have a hyperchloraemic acidosis, with little or no increase in blood-urea concentration. The urine at the time was relatively alkaline (pH 6·5 to 7·4). In addition, nine of the 11 patients had generalized nephrocalcinosis, of which a typical example is shown in Plate 19, Fig. 17. The renal abnormality

in this syndrome is usually thought to be purely tubular, and Albright has coined the term 'tubular-insufficiency-without-glomerular-insufficiency' to describe it. Table V shows that this is an over-simplification, for every patient of this group (which in view of its size is probably representative) was shown by reduced clearances of urea and endogenous creatinine to have impaired glomerular function, although usually insufficient to cause appreciable nitrogen retention. Five of these patients were originally potassium-depleted, but only one (Subject 33) had symptoms of potassium depletion at the time of the present study. Two others, who had not yet been treated with alkalis (Subjects 29 and 30), had a moderate hypokalaemia, without symptoms. The remainder had neither symptoms nor biochemical evidence of potassium depletion—a point of some importance in view of the known effect of potassium deficiency on the excretion of acid.

When studied, the majority of these patients had been receiving treatment with alkalis for months or years. This treatment was stopped at least five days before the test dose of ammonium chloride was given, except in the case of Subjects 36 and 37, who were allowed to continue treatment until the day before the study. The response of these two patients to ammonium chloride was a little different from that of the other nine, chiefly in the lower rate of ammonium excretion. Data from these two patients have therefore been excluded from Figs. 6 and 7, but the main features of their response are shown in Table V. Data from Subject 33 are also omitted from Figs. 6 and 7, as in her case only a single pooled specimen of urine was collected from two to eight hours after ingestion of ammonium chloride.

The main features of the response to ammonium chloride in this group was as follows (Figs. 6 to 8; Table V). Urinary *pH* usually remained between 6·4 and 7·0, but Subject 28 was able to excrete urine of pH 5·67. Excretion of *titratable acid* was greatly reduced, and, in keeping with the high pH of these urines (see Fig. 2), phosphate accounted for nearly all of the titratable acidity (mean 80 per cent.). Ammonium excretion was also reduced, except in the case of Subject 29, and there was a normal relationship between urinary ammonium and pH (Fig. 7). As a result of the reduced excretion of both titratable acid and ammonium, and appreciable excretion of bicarbonate in all patients except Subject 28, excretion of total *hydrogen ion* was very greatly reduced. In an attempt to discover whether there was a limitation in the excretion of titratable acid *per se*, Subject 34 was given ammonium chloride on a second occasion during the intravenous infusion of isotonic sodium phosphate (pH 7·4). The average urinary pH during the infusion was 6·63, not significantly different from the figure recorded after ammonium chloride alone (pH 6·69). Fig. 8 shows that the excretion of titratable acid was enormously increased, and was proportional to the excretion of phosphate. Thus in this patient, as in the normal individual, excretion of titratable acid appeared to be limited only by the rate of buffer excretion and the minimum urinary pH; because the latter was abnormally high, less titratable acid than normal could be excreted at the usual level of buffer excretion.


NH4 Cl
7·0
6·0
5·0
4·0
pH
30
(a)
NH4 Cl
60
40
20
Titratable acid (μ-equiv./min.)
(b)

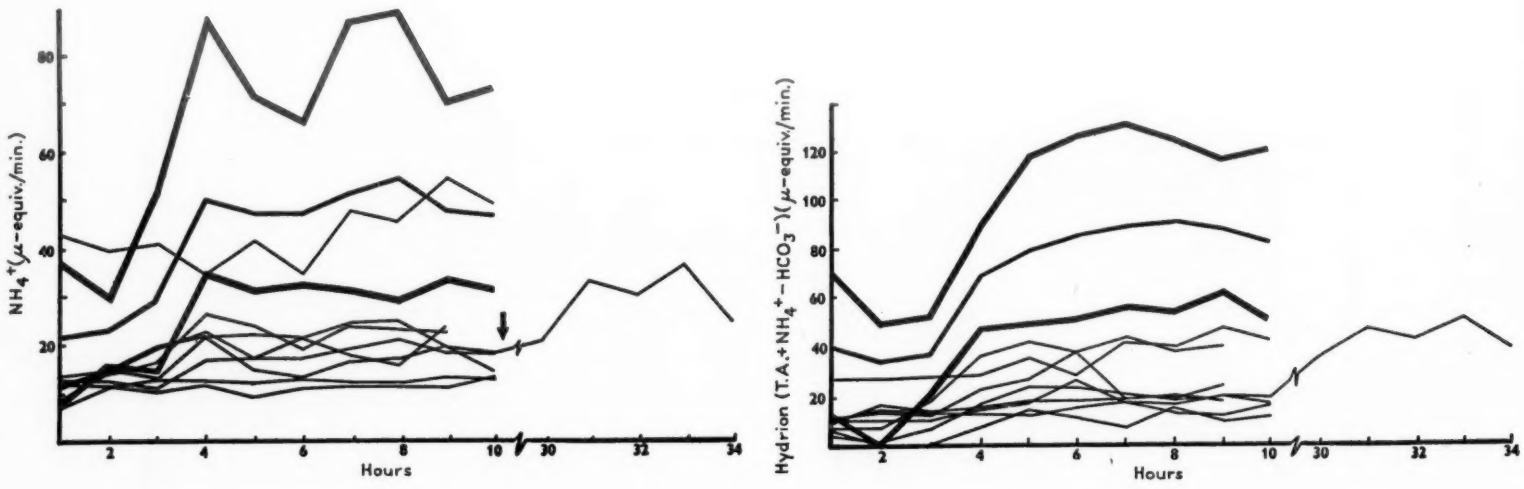


FIG. 6. Renal tubular acidosis: excretion of acid after administration of ammonium chloride. Subject 30 was given a further dose of ammonium chloride (10 g.), as shown by the arrow.

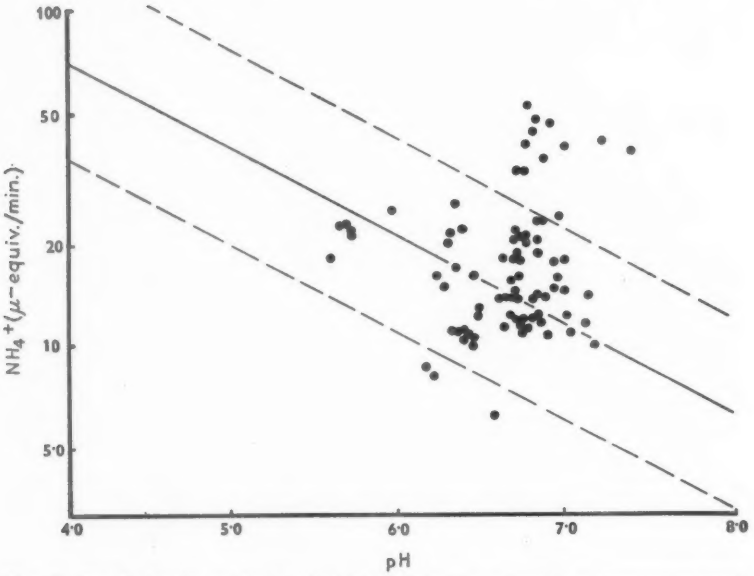


FIG. 7. Renal tubular acidosis: relationship between excretion of ammonium and urinary pH.

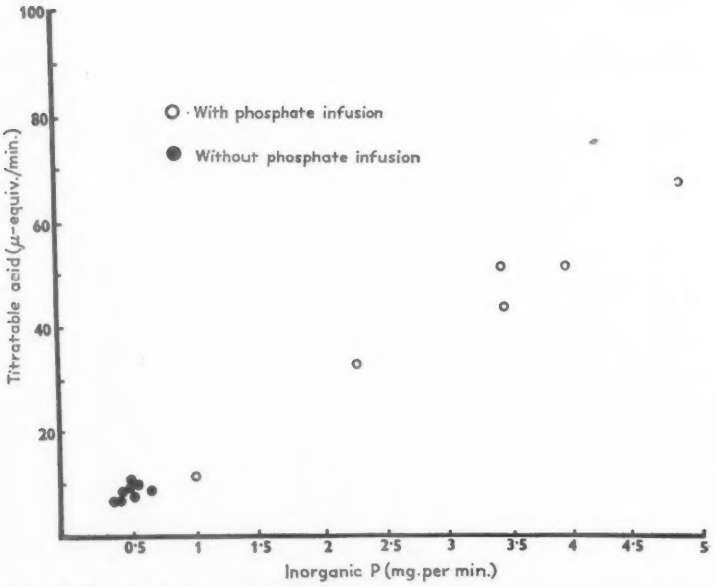


FIG. 8. Renal tubular acidosis, Subject 34. The effect of intravenous infusion of phosphate on the excretion of titratable acid and phosphate (expressed as phosphorus).

TABLE V

Renal Tubular Acidosis

						Plasma, before NH_4Cl					*Urine, 2–8 hours after NH_4Cl*						
Subject	*Age at time of study*	*Sex*	*Weight (kg.)*	*Endogenous creatinine clearance (ml./min.)*	*Urea clearance (% of normal)*	*Urea (mg./100 ml.)*	*Total CO_2 (m-moles/l.)*	*Cl (m-equiv./l.)*	*K (m-equiv./l.)*	*Inorganic P (mg./100 ml.)*	*pH*	*Titratable acid (μ-equiv./min.)*	*Inorganic P (mg./min.)*	*% of titratable acid due to P*	*NH_4^+ (μ-equiv./min.)*	*HCO_3^- (μ-equiv./min.)*	*Total H^+ (μ-equiv./min.)*
27	12	M	41	46	28	34	21·7	108	3·6	4·2	6·96	3·9	0·55	97	18	..	11
28	25	F	48	55	54	22	26·3	106	4·4	3·8	5·67	18	0·56	73	22	⩽1·0	40
29	39	M	59	56	49	35	17·8	113	3·3	2·1	6·81	12	0·89	72	44	22	39
30	40	M	51	46	39	37	22·8	105	3·2	4·0	6·76	10	0·82	86	23	10	21
31	42	M	69	60	36	43	24·2	98	4·1	2·9	6·31	18	0·84	83	19	..	25
32	48	F	41	26	29	53	23·5	105	3·9	2·8	6·40	12	0·64	89	11	4·6	19
33	51	F	50	27	27	44	20·6	111	2·4	3·1	6·83	9	0·71	82	22	11	20
34	52	F	51	21	26	43	21·4	110	3·8	3·0	6·69	10	0·50	59	16	8·0	17
35	60	M	41	24	28	51	17·5	108	4·4	3·7	6·75	5·8	0·44	81	10	6·5	14
										Range	5·67–6·96	4–18	0·44–0·89	59–97	10–44	..	11–40
36	40	F	74	61	67	38	26·2	93	3·9	2·8	6·94	10	0·96	69	19	30	6
37	43	F	58	57	32	33	29·9	98	4·2	3·4	6·86	8·5	0·71	73	13	15	11

It has sometimes been suggested that the hyperchloraemia of renal tubular acidosis is partly a result of a specific inability to excrete chloride. The experiments here recorded, although not designed to settle this point, suggest that this is not the case. Fig. 9 shows that after stimulation by ammonium chloride the excretion of chloride increased as much as it did in patients with general renal failure. The increase in the rate of chloride excretion was proportional to the glomerular filtration rate in both groups of patients.

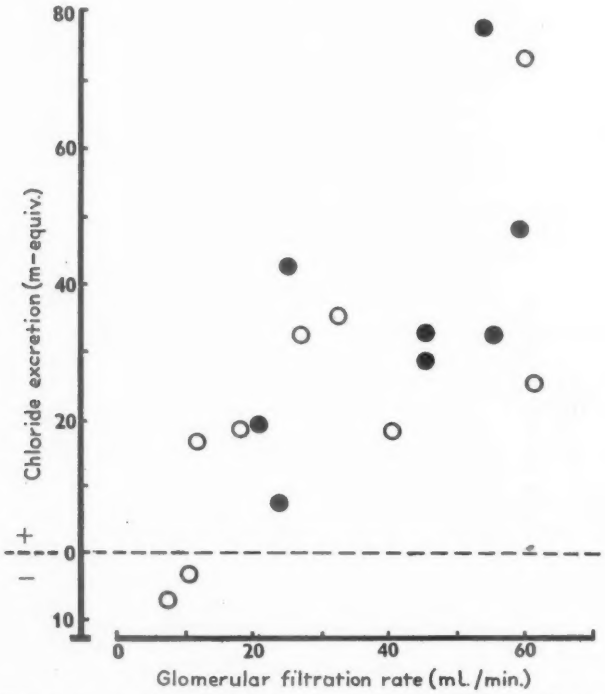


FIG. 9. Renal tubular acidosis and general renal failure: effect of ammonium chloride on the excretion of chloride.

Open symbols, general renal failure (Subjects 11–19); solid symbols, renal tubular acidosis (Subjects 27–35). The ordinate shows the total increment in chloride excretion, over the average of two control values, from 0 to eight hours after administration of ammonium chloride. The endogenous creatinine clearance is used as a measure of glomerular filtration.

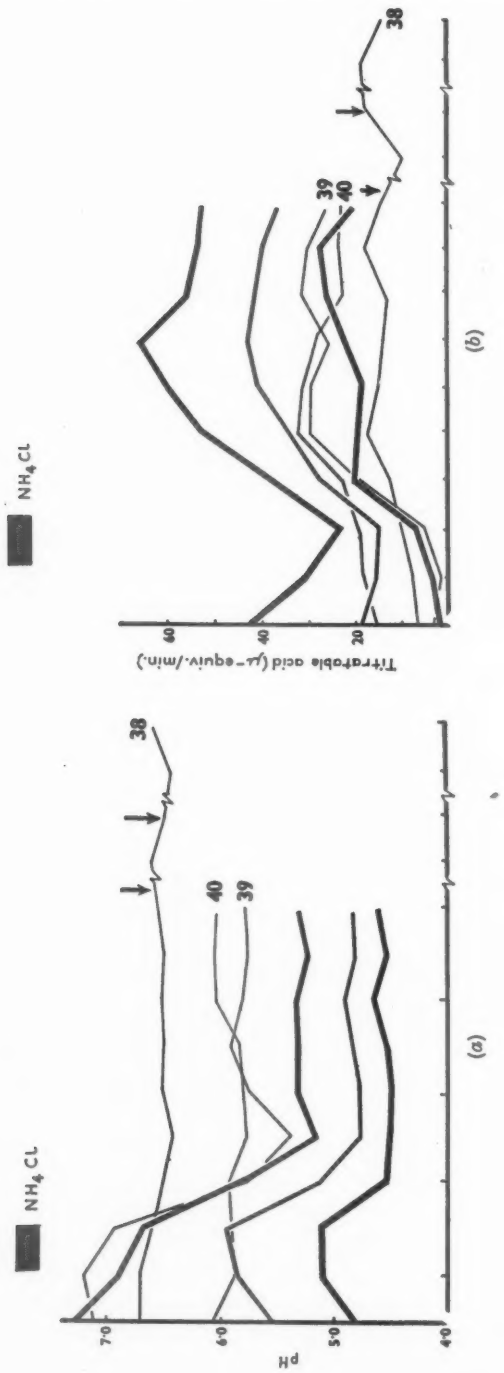
In summary, these patients were unable to excrete urine of normal minimum pH, and as a consequence their excretion of titratable acid was reduced. In addition, all except one had a low rate of ammonium excretion. Except in one case, the urine contained appreciable amounts of bicarbonate, further contributing to the low excretion of total hydrogen ion.

Incomplete form of renal tubular acidosis. One of the main purposes of the present study was to discover, if possible, subjects who had the tubular lesion

TABLE VI

Incomplete Syndrome of Renal Tubular Acidosis

Subject	Age	Sex	Weight (kg.)	Average urinary excretion of calcium (mg./day)	Endogenous creatinine clearance (ml./min.)	Urea clearance (% of normal)	*Plasma, before NH_4Cl*						*Urine, 2–8 hours after NH_4Cl*							
							Urea (mg./100 ml.)	Total CO_2 (m-moles/L.)	Cl (m-equiv./L.)	K (m-equiv./L.)	Inorganic P (mg./100 ml.)	pH	Titratable acid (μ-equiv./min.)	Inorganic P (mg./min.)	% of titratable acid due to P	NH_4^+ (μ-equiv./min.)	HCO_3^- (μ-equiv./min.)	Total H^+ (μ-equiv./min.)
38	44	M	75	140	98	63	34	28·4	103	4·2	4·5	6·50	15	0·76	76	44	7·0	54
39	30	M	68	230	53	66	22	27·7	101	4·1	3·2	5·73	28	0·70	58	79	1·0	107
40	39	M	62	110	79	57	36	28·9	104	4·5	3·6	5·91	26	0·86	73	103	1·0	129
																	<	<


NH4 Cl
pH
7·0
6·0
5·0
4·0
38
40
39
(a)
NH4 Cl
Titratable acid (μ-equiv./min.)
60
40
20
38
39
40
(b)

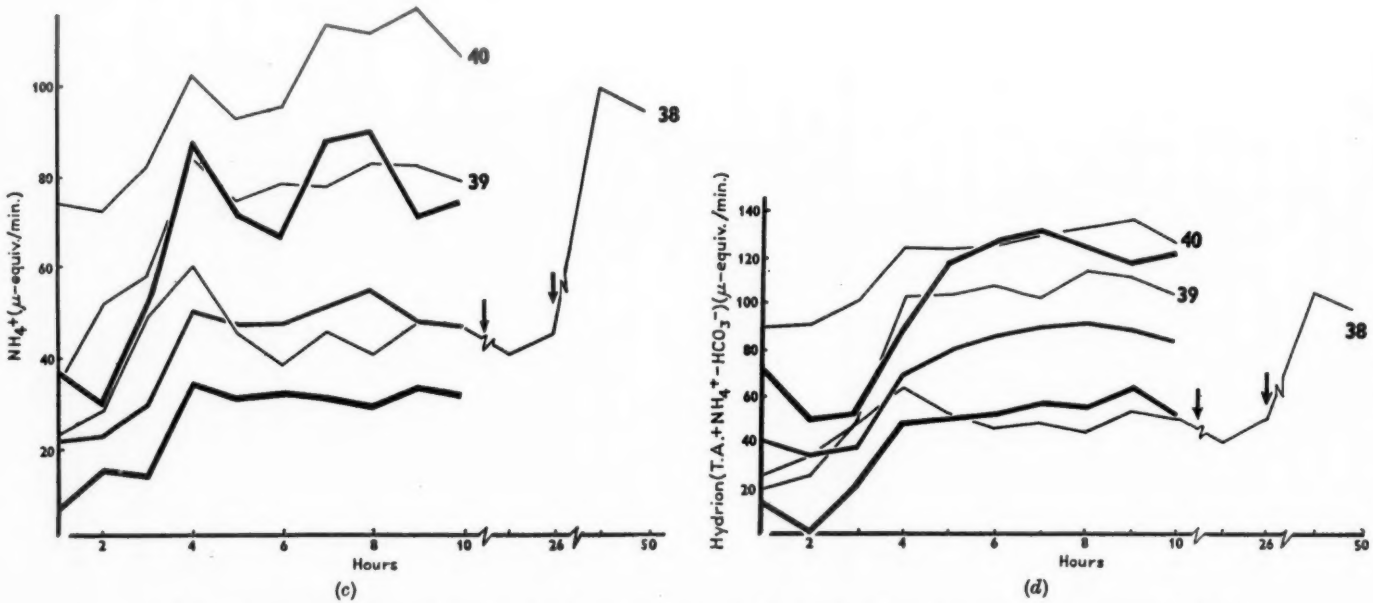


FIG. 10. Incomplete syndrome of renal tubular acidosis: excretion of acid after administration of ammonium chloride. Subject 38 was given two further doses of ammonium chloride, totalling 23 g. in all, shown by the arrows.

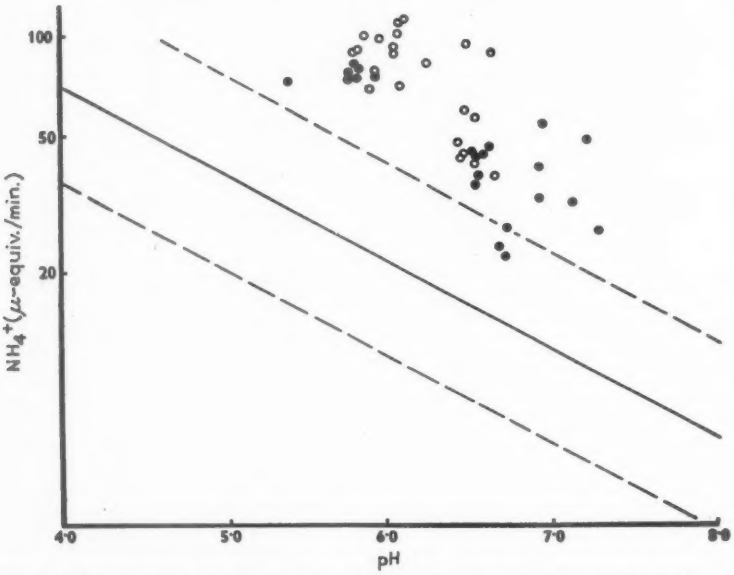


FIG. 11. Incomplete syndrome of renal tubular acidosis: relationship between excretion of ammonium and urinary pH.

Open symbols show data obtained after additional doses of ammonium chloride.

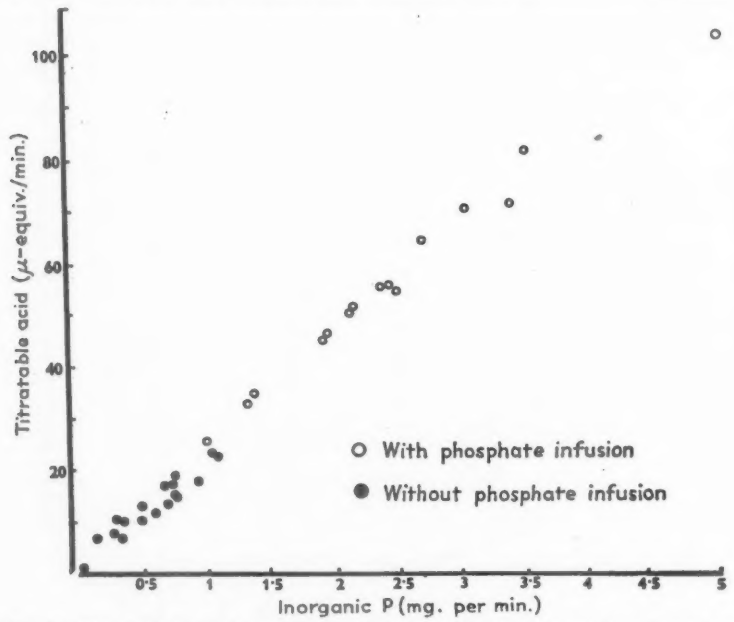


FIG. 12. Incomplete syndrome of renal tubular acidosis (Subject 38). The effect of intravenous infusion of phosphate on the excretion of titratable acid and phosphate.

of renal tubular acidosis in a form insufficiently severe to cause an acidosis. We have to date studied three patients whom we believe to have this syndrome; in each case a renal tubular lesion was initially suspected because of the discovery of diffuse renal calcification. Detailed reports of these patients are given in Appendix II, and here only the main features of the syndrome are discussed. All three patients were in good general health, and it was something relatively trivial which led to the discovery of nephrocalcinosis—in the first case a short-lived episode of haematuria, in the second the finding of proteinuria at a routine examination, and in the third an attack of renal colic. The pattern of intrarenal calcification was the same in all three (Plate 19, Fig. 18; Plate 20, Figs. 19 and 20), showing flecks of calcium clustered in the position of the medullary pyramids. This is the usual form of nephrocalcinosis seen in renal tubular acidosis, although a similar pattern occurs in other diseases, such as primary hyperparathyroidism and vitamin-D intoxication. But these patients did not have acidosis, and there was no reason to suspect any of the other causes of nephrocalcinosis: there was no story of excessive intake of alkalis or vitamin D and no evidence of bone disease, and the blood-urea and plasma-electrolyte concentrations were repeatedly found to be normal. In addition, all three were excreting normal amounts of calcium in the urine—under 300 mg. daily while taking a normal diet (Pyrah, 1958)—whereas in our experience most patients with nephrocalcinosis have a definite hypercalcuria.

Their response to ammonium chloride (Figs. 10 to 12; Table VI) was similar to that of patients with renal tubular acidosis, but with some important differences. The urinary *pH* did not fall into the normal minimum range, but remained between 5·7 and 6·5; Subject 38 was given two further doses of ammonium chloride within 24 hours of the first (23 g. in all), but there was no further fall in urinary pH. Phosphate buffer was excreted at a normal rate, and therefore excretion of *titratable acid* was rather low. But excretion of *ammonium* was not impaired, and in at least one case was increased above normal; consequently all three patients excreted abnormally large amounts of ammonium for their urinary pH (Fig. 11). Total excretion of *hydrogen ion* was normal or only slightly reduced, mainly as a result of the large contribution made by ammonium.

Two of these patients were given very large doses of ammonium chloride and rapidly recovered from the resultant acidosis, showing how efficient their excretion of hydrogen ion—mainly ammonium—could be. Subject 38 took 23 g. during the course of a day, and four days later the total CO_2 concentration in the plasma was normal. Subject 40 was given 34 g. in four days; on the fourth day of administration the plasma total CO_2 was only slightly diminished (22·2 m-moles per litre), and three days later it had returned to normal. Subject 38 was also given our standard dose of ammonium chloride during intravenous infusion of isotonic sodium phosphate, pH 7·4. Urinary pH was not appreciably altered by this procedure, but phosphate excretion was enormously increased and the excretion of titratable acid increased in proportion (Fig. 12). Thus in this patient, as in Subject 34 with renal tubular acidosis, there appeared to be

TABLE VII

Generalized Nephrocalcinosis and Bilateral Renal Calculi

							Plasma, before NH_4Cl			*Urine, 2–3 hours after NH_4Cl*				
Subject	*Age*	*Sex*	*Weight (kg.)*	*Average urinary excretion of calcium (mg./day)*	*Endogenous creatinine clearance (ml./min.)*	*Urea clearance (% of normal)*	*Urea (mg./100 ml.)*	*Calcium (mg./100 ml.)*	*Inorganic P (mg./100 ml.)*	*pH*	*Titratable acid (μ-equiv./min.)*	*NH_4^+ (μ-equiv./min.)*	*Total H^+ (μ-equiv./min.)*	*Diagnosis*
Generalized nephrocalcinosis:														
41	22	M	80	410	44	48	31	10·5	1·8–2·8	5·43	27	47	74	? Hyperparathyroidism
42	29	M	70	320	93	137	28	10·8–11·0	3·2–4·0	5·09	43	55	98	? Hyperparathyroidism
43	30	M	64	230	53	91	26	10·5	3·2	4·80	39	76	105	Idiopathic hypercalcuria
44	34	M	66	380	82	90	31	10·6	2·8	5·03	36	90	126	Milk-alkali syndrome
45	36	M	60	370	..	69	36	10·0–11·0	3·4–4·2	5·00	35	47	82	? Hyperparathyroidism
46	59	M	61	300	74	54	36	11·0–11·2	3·4	5·44	24	65	89	? Hyperparathyroidism
Bilateral renal calculi:														
47	33	M	80	430	90	103	27	10·6	3·4	4·63	49	47	96	Idiopathic hypercalcuria
48	34	F	57	435	..	..	24	9·2	3·9	4·80	51	55	106	Idiopathic hypercalcuria
49	35	F	56	440	..	..	32	9·8–10·8	3·3–4·0	5·07	35	38	73	Idiopathic hypercalcuria
50	35	M	67	380	..	..	30	10·8–11·5	2·8	4·89	..	..	..	? Hyperparathyroidism

TABLE VIII

Severe Potassium Depletion

Subject	*Age*	*Sex*	*Weight (kg.)*	*Endogenous creatinine clearance (ml./min.)*	*Urea clearance (% of normal)*	*Plasma, before NH_4Cl*							*Urine, 2–8 hours after NH_4Cl*							*Diagnosis*
						Urea (mg./100 ml.)	*Total CO_2 (m-moles/l.)*	*Cl (m-equiv./l.)*	*K (m-equiv./l.)*	*Na (m-equiv./l.)*	*Inorganic P (mg./100ml.)*	*pH*	*Titratable acid (μ-equiv./min.)*	*Inorganic P (mg./min.)*	*% of titratable acid due to P*	*NH_4^+ (μ-equiv./min.)*	*HCO_3^- (μ-equiv./min.)*	*Total H^+ (μ-equiv./min.)*	
51	48	F	35	29	38	32	29·6	100	2·3	144	3·5	5·87	9·5	0·31	73	28	<1·0	38	Potassium-losing renal disease
52	52	M	46	41	43	21	42·2	79	2·6	128	3·4	6·19	20	0·74	69	67	7·1	81	Hyperaldosteronism and unilateral renal disease
53	58	F	44	43	73	24	29·1	102	1·9	142	2·8	5·52	16	0·18	27	49	<1·0	65	Idiopathic steatorrhoea

no limitation in the excretion of titratable acid *per se*. The slope of the line of points in Fig. 12 is steeper than that in Fig. 8 because this patient could excrete a slightly more acid urine than Subject 34, and so could make more complete use of urinary buffer in excreting titratable acid.

In summary, these patients resembled those with renal tubular acidosis in that they were unable to excrete a highly acid urine. But, unlike patients with tubular acidosis, they were able to excrete large quantities of ammonium, and because of this could quickly correct an artificial acidosis.

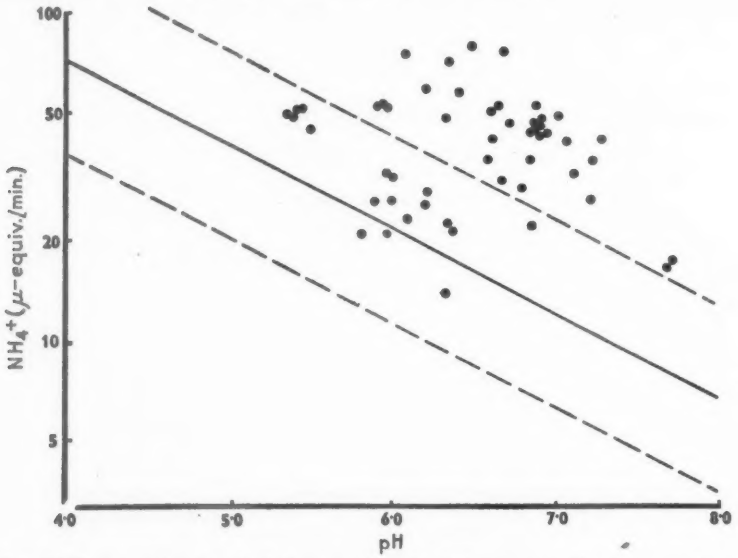


FIG. 13. Severe potassium depletion: relationship between excretion of ammonium and urinary pH.

Unexplained generalized nephrocalcinosis. Six other patients with nephrocalcinosis were given ammonium chloride (Table VII); their response was normal, except that two (Subjects 41 and 46), both probably suffering from primary hyperparathyroidism, were unable to excrete urine of normal minimum pH. The abnormality was very slight (pH 5·43 and 5·44 instead of 5·3 and under) and similar to that observed in other patients with proved hyperparathyroidism (see below, page 289). The majority of these patients were excreting excessive amounts of calcium in their urine, unlike the three patients with the incomplete form of renal tubular acidosis. Four patients with *bilateral renal calculi* and hypercalcuria were also studied, but their excretion of acid was entirely normal (Table VII).

Severe potassium depletion. Under this heading we have included only patients whose main symptoms were those of potassium deficiency. Three patients were studied: in two potassium deficiency arose from excessive urinary loss (in one case as a result of hyperaldosteronism), and in the third from faecal loss as a result of steatorrhoea. Clinical details are given in Appendix II. The responses

of these three patients to ammonium chloride were similar (Table VIII). All were unable to excrete urine of normal minimum pH, but their excretion of ammonium was little impaired, and was abnormally great for the pH of their urine (Fig. 13). Consequently their excretion of total hydrogen ion was only slightly reduced, and they rapidly corrected the acidosis produced by this test. In these respects their response was strikingly similar to that of the three patients with the incomplete syndrome of renal tubular acidosis. An unexpected feature of the response of these patients was their failure to increase chloride excretion appreciably (Table IX). Normal subjects respond to ammonium chloride by a brisk chloride diuresis and an increase in the excretion of sodium

TABLE IX

Severe Potassium Depletion: Excretion of Electrolytes Before and 2–8 Hours After Administration of NH_4Cl

	Urinary excretion rates (μ-equiv./min.)							
	Cl		*Na*		*K*		NH_4	
Subject	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
2 (normal)	90	369	57	190	41	152	20	51
14 (general renal failure)	90	124	73	86	39	51	11	14
51	8	18	4	4	5	7	11	28
52	29	98	30	62	29	36	37	67
53	78	83	97	71	25	16	22	49

and potassium; initially ammonium accounts for very little of the extra chloride excreted (Gamble, Blackfan, and Hamilton, 1925). This has been our experience, and we have found that the diuresis of chloride, sodium, and potassium is much reduced in advanced glomerular failure (see also Fig. 9). The three potassium-depleted subjects, although their glomerular filtration rates were not greatly reduced, showed little increase in the excretion of these three ions, and in one study (Subject 53) no appreciable change at all. Collections of urine were made over the succeeding 24 hours, and showed no nocturnal diuresis of chloride. The inverted diurnal rhythm of electrolyte excretion previously reported in potassium depletion (Mahler and Stanbury, 1956) does not here explain the absence of an immediate chloride diuresis.

Prolonged hypercalcaemia. Ten patients were studied (Table X). Eight had primary hyperparathyroidism, proved by the surgical removal of a parathyroid adenoma, one had vitamin-D intoxication, and one had myelomatosis with extensive bone disease. Although none of these patients had a systemic acidosis, the short test with ammonium chloride showed that five of them were unable to excrete urine of normal minimum pH (Subjects 56, 57, 60, 62, and 63). The abnormality was not very marked except in the case of Subject 57, who excreted urine of pH 7·04 after ammonium chloride. This patient also had a symptomless hypokalaemia, and considerably impaired powers of urinary concentration. Her impairment of urinary acidification was more marked than we have seen in potassium depletion alone, and tubular damage resulting from persistent

TABLE X

Hypercalcaemic Subjects

Subject	*Age*	*Sex*	*Weight (kg.)*	*Probable duration of hypercalcaemia (years)*	*Endogenous creatinine clearance (ml./min.)*	*Urea clearance (% of normal)*	*Plasma, before NH_4Cl*					*Urine, 2–8 hours after NH_4Cl*						*Maximum urinary osmolarity after pitressin or 14–18 hours of dehydration (m-osmoles/l.)*	*Remarks*
							Urea (mg./100 ml.)	*Total CO_2 (m-moles/l.)*	*K (m-equiv./l.)*	*Calcium (mg./100 ml.)*	*Inorganic P (mg./100 ml.)*	*pH*	*Titratable acid (μ-equiv./min.)*	*Inorganic P (mg./min.)*	*% of titratable acid due to P*	*NH_4^+ (μ-equiv./min.)*	*Total H^+ (μ-equiv./min.)*		
Primary hyperparathyroidism:																			
54	14	M	43	3	41	57	36	29	3·7	9·5 (21·0 pre-op.)	5·8	4·67	23	0·39	41	24	47	751	Bone disease; studied 4 months after operation
55	49	F	59	2	44	..	34	26	3·6	12·7	1·5	4·94	33	0·64	48	57	91	474	Bone disease
56	50	F	57	35	46	53	34	27	3·9	12·2	3·1	5·76	25	..	..	35	60	575	Bilateral renal calculi and slight nephrocalcinosis
57	52	F	35	6	24 (inulin)	28	50	26	2·6	13·4	2·6	7·04	3·6	0·41	61	16	10	340	Renal calculi and bone disease
58	54	F	43	7	49	35	43	27	3·8	9·0 (12·0 pre-op.)	3·0	5·10	58	0·035	15	26	32	586	Bone disease; studied 5 weeks after operation
59	65	F	44	3	40	62	34	29	4·3	13·0	2·0	4·83	26	0·68	65	31	57	529	Bone disease
60	66	F	30	2	17	28	39	27	4·2	15·0	2·7	5·82	16	0·45	62	21	38	408	Bone disease
61	75	F	57	16	62	56	30	27	4·7	12·8	2·6	5·19	26	0·61	58	59	85	690	Bone disease and renal calculi
Vitamin-D intoxication:																			
62	58	M	56	$\frac{4}{12}$	18	26	86	23·4	3·3	12·2	4·7	5·72	26	0·58	53	16	42	..	Idiopathic hypoparathyroidism; excessive vitamin-D medication
Multiple myeloma:																			
63	45	F	46	$\frac{8}{12}$	..	..	44	29·0	4·0	17·6	4·1	5·40	..	..	..	..	..	..	Extensive bone lesions

TABLE XI

Patients Recovering from Anuria or with Adult Fanconi Syndrome

Subject	Age	Sex	Endogenous creatinine clearance (ml./min.)	Urea clearance (% of normal)	Plasma, before NH_4Cl: Urea (mg./100 ml.)	Total CO_2 (m-moles/l.)	Cl (m-equiv./l.)	K (m-equiv./l.)	Inorganic P (mg./100 ml.)	Urine, 2–8 hours after NH_4Cl: pH	Titratable acid (μ-equiv./min.)	Inorganic P (mg./min.)	NH_4^+ (μ-equiv./min.)	HCO_3^- (μ-equiv./min.)	Total H^+ (μ-equiv./min.)	Maximum urinary osmolarity (m-osmoles/l.)	Remarks
Acute anuria:																	
64	36	F	46 (22)	22	81	31·3	88	3·5	4·9	6·39	13	0·54	10·7	..	22	..	10 days after diuresis commenced
			(52)	46	35	29·8	98	4·1	..	6·15	15	0·53	35	..	55	..	16 days „ „
65	32	F	41	50	106	26	..	96	4·4	..	4·87	18	..	42	..	60	790	11 weeks „ „
66	52	M	78	89	57	39	31·8	108	3·7	4·0	4·79	34	0·77	31	..	65	365	10 months „ „
Fanconi syndrome:																	
67	47	F	40	49	..	30	33·7	96	2·3	1·8	6·84	9·3	0·53	47	19	45	..	..
68	65	M	49	8·6	14	109	16·2	112	3·6	..	5·55	12	0·34	3·8	..	16	329	Myelomatosis

hypercalcaemia seems a more likely cause. Cohen, Fitzgerald, Fourman, Griffiths, and de Wardener (1957) have recently reported a similar patient who had hyperparathyroidism and impaired urinary acidification, but no evidence of potassium depletion. It is worth noting that only one of these five patients who were unable to excrete a maximally acid urine (Subject 56, with the longest history) had radiologically visible nephrocalcinosis, and it was very slight. Their lack of generalized nephrocalcinosis and definite hypercalcaemia clearly distinguished these patients from those with the incomplete syndrome of renal tubular acidosis.

Recovery from acute anuria (Table XI; Appendix II). Three patients were studied. Only one (Subject 64) was seen in the immediate post-anuric diuretic phase of the disease, and she alone showed an abnormal response to ammonium chloride. She was tested on the 10th day of diuresis, and her urinary pH fell only to 6·39; the glomerular filtration rate was still very low, which might explain the impaired excretion of ammonium at this time. Six days later she was given ammonium chloride again; urinary pH had improved very slightly (6·15), whereas filtration rate and excretion of ammonium had both more than doubled. These observations support the findings of de Oliveira (1953) that during the diuretic stage of recovery the ability to excrete ammonium may recover before ability to excrete highly acid urine.

Fanconi syndrome (Table XI; Appendix II). Two patients with the rare adult form of this syndrome were studied. Clinically they were quite dissimilar. In Subject 67 the effects of the tubular lesion, chiefly potassium depletion, dominated the clinical picture, and renal excretory function was not seriously impaired; Subject 68 suffered from severe renal failure with uraemia, and his tubular abnormality was a chance finding of little practical importance. The two patients responded in different fashions to ammonium chloride. Subject 67 reacted like other potassium-depleted subjects in failing to excrete urine of low pH, although excretion of ammonium was well preserved; Subject 68 excreted almost as acid a urine (pH 5·55) as did normal subjects, but excretion of ammonium was markedly reduced, a response similar to that of other patients with generalized renal failure.

The excretion of bicarbonate. Urinary bicarbonate was measured in many of these studies. Specimens more acid than pH 6·0 contained negligible amounts (Fig. 14), but above this pH the concentration of bicarbonate rose steeply. Many of the relatively alkaline specimens from normal subjects had very high concentrations of bicarbonate, indicating a urinary pCO_2 considerably above that of venous blood—an observation previously made by Pitts, Ayer, and Schiess (1949). Urine of similar pH from patients with the syndrome of renal tubular acidosis, both complete and incomplete, contained much less bicarbonate, implying a urinary pCO_2 either close to, or less than, that of venous blood. Unfortunately no urine specimens of this pH from patients with generalized renal disease were available for comparison. Urinary bicarbonate represents base lost from the body, and its excessive excretion in some forms of renal disease is often regarded as an important factor in the causation of acidosis. In the present

study, however, urinary bicarbonate was quantitatively the least important of the three factors contributing to the excretion of total hydrogen ion (ammonium *plus* titratable acid *minus* bicarbonate). The highest figure of bicarbonate excretion encountered after administration of ammonium chloride was 30 μ-equiv. per minute, from Subject 36, a patient with renal tubular acidosis. Other patients with this syndrome excreted less bicarbonate, and in three cases (Subjects 28, 39, and 40) less than 1 μ-equiv. per minute.

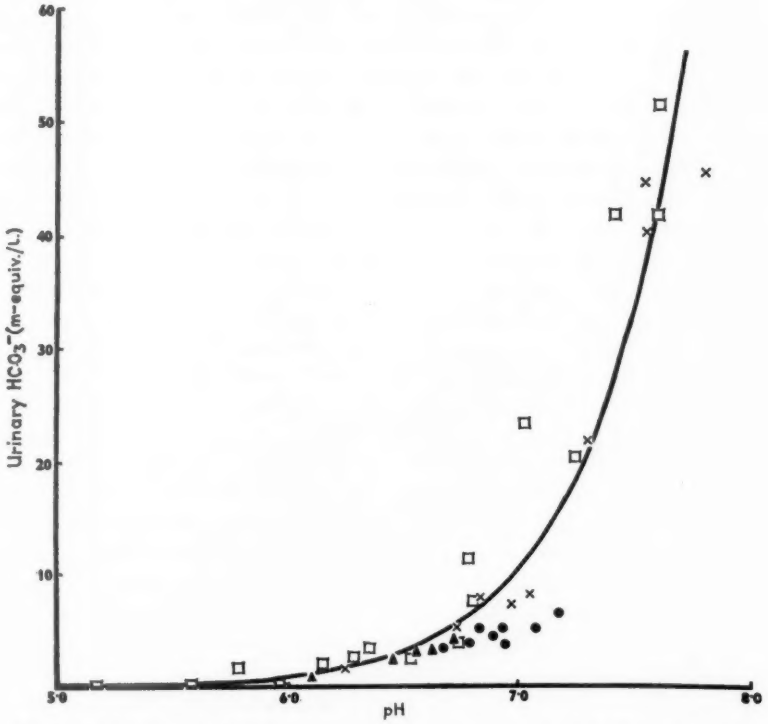


FIG. 14. The relationship of urinary bicarbonate concentration to urinary pH.

□ Normal subjects.
● Renal tubular acidosis.
▲ Incomplete syndrome of renal tubular acidosis.
× Potassium depletion.

Representative data from male subjects only (Nos. 1, 3, 5, 8, 29, 30, 35, 38, and 52). The continuous line was calculated from the Henderson–Hasselbalch equation assuming a constant urinary pCO_2 of 45 mm. Hg.

Excretion of ammonium (all subjects). When information from all the subjects of the present study was compared it was apparent that ability to excrete ammonium depended more on the severity of glomerular damage than on the exact type of renal disease. Fig. 15 shows a definite relationship between the excretion of ammonium after administration of ammonium chloride and the

glomerular filtration rate. Impaired excretion of ammonium in nine patients with renal tubular acidosis and two with the Fanconi syndrome did not appear to be due to the specific tubular defects of these syndromes, for these patients excreted as much ammonium as did patients with other forms of renal disease and comparable filtration rates. The relationship shown in Fig. 15 also helps to explain the existence of an 'incomplete form' of renal tubular acidosis, for the normal excretion of ammonium by these three patients was associated with normal or nearly normal glomerular filtration rates.

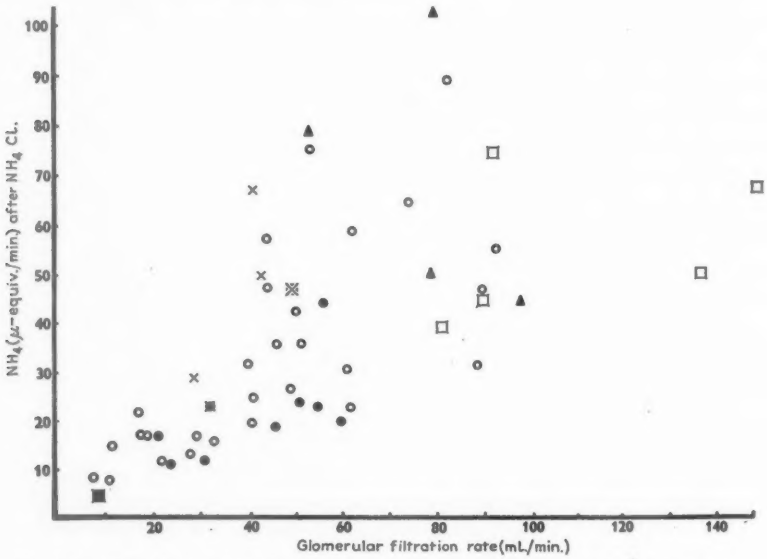


FIG. 15. All subjects: the relationship of ammonium excretion, after administration of ammonium chloride, to the glomerular filtration rate.

□ Normal subjects. ● Renal tubular acidosis. ▲ Incomplete syndrome of renal tubular acidosis. × Severe potassium depletion. ■ Fanconi syndrome. ○ Other forms of renal disease.

Subjects 40 (incomplete renal tubular acidosis) and 64 (recovery from acute anuria) were studied twice, but otherwise each point represents a separate patient. Subjects 33 (renal tubular acidosis) and 67 (Fanconi syndrome) were also severely depleted of potassium, and are shown as composite symbols.

Discussion

The validity of a short test in the assessment of acid-excretion. In the investigation of abnormalities of acid-excretion a short test such as that described here has many practical advantages over the longer procedure used by Albright and others. The chief gain is an immense saving of time and trouble. The test is more pleasant for patients, for it does not require admission to hospital or dietary restrictions. In addition, because a smaller dose of ammonium chloride is used, there is less risk of inducing severe acidosis and electrolyte depletion in

patients with renal disease. It is important, however, to decide how completely this test stimulates the excretion of acid, and to compare it in this respect with the longer procedure. The short test appears to give a reliable estimate of a subject's ability to lower the urinary pH (on which the excretion of titratable acid and bicarbonate largely depends); for our 10 normal subjects passed urine of pH ranging from 4·60 to 5·24, which compares favourably with the pH 4·49 to 5·34 accomplished by Pitts's normal subjects in acute acidosis following ingestion of three times the amount of ammonium chloride (Pitts, Lotspeich, Schiess, and Ayer, 1948; Pitts, Ayer, and Schiess, 1949). Moreover, an acute acidosis is known to be more effective than a sustained one in lowering the urinary pH, for, when ammonium chloride is given for several days, the urinary pH is usually lowest on the first or second day and thereafter gradually rises (Sartorius, Roemmelt, and Pitts, 1949; Wood, 1955)—a change which Milne, Muehrcke, and Heard (1957) have suggested is the result of progressive potassium depletion. Our results in patients with renal disease suggest that here, too, no further fall in urinary pH is to be expected when experimental acidosis is maintained for several days. On the other hand, the excretion of ammonium does not appear to be maximally stimulated by the test we have described. Normal subjects excreted 33 to 75 μ-equiv. per minute, appreciably less than the 105 to 180 μ-equiv. per minute (150 to 250 m-equiv. daily) which can be achieved by subjects taking ammonium chloride in similar daily dosage for several days (Sartorius, Roemmelt, and Pitts, 1949; Wood, 1955). Probably from three to seven days of sustained acidosis are necessary to stimulate the excretion of ammonium to the full (Gamble, Blackfan, and Hamilton, 1925; Farquharson, Salter, Tibbetts, and Aub, 1931). This slow rise in the excretion of ammonium is sometimes attributed to a slow increase in renal glutaminase, which is known to occur in similar circumstances in the rat (Davies and Yudkin, 1952; Rector, Seldin, and Copenhaver, 1955), but it is not certain that this happens in the human kidney. The evidence therefore suggests that a short test of acid-excretion, such as we have used here, is a reliable procedure for determining the minimum urinary pH which the kidneys can achieve, but probably does not cause maximum excretion of ammonium. Failure to stimulate excretion of ammonium fully may be of little importance in a test of *tubular* function, for the results of the present study suggest that impaired excretion of ammonium is a sign of generalized renal failure, and can be predicted whenever there is other evidence of renal excretory impairment (Fig. 15).

Limitation of urinary pH and ammonium in renal disease. The present study showed that the kidney's ability to excrete urine of low pH and its ability to excrete ammonium are independently affected by different forms of renal disease. Excretion of an acid urine was impaired in a few well-defined tubular syndromes—renal tubular acidosis, severe depletion of potassium, and during recovery from acute anuria—but not in most patients with renal excretory failure and uraemia. On the other hand ability to excrete ammonium was closely related to renal excretory function, as measured by creatinine and urea clearances, and did not appear to be specifically impaired in these tubular syndromes

(Fig. 15). This dissociation is surprising in view of the overwhelming evidence that both the acidification of the urine and the production of urinary ammonium are tubular functions. A possible explanation is that ammonium is formed in a part of the tubule which does not secrete free hydrogen ion and is not affected by these tubular diseases—perhaps the collecting ducts (as suggested by observations of Richterich-van Baerle, Goldstein, and Dearborn, 1956); alternatively, the capacity of renal tubular cells to form ammonium may survive when some of their other functions, such as the excretion of hydrogen ion against a concentration gradient, are lost. The relationship between glomerular filtration and capacity to excrete ammonium appears more easily explained, for the function of the renal tubules clearly depends on the integrity of the glomeruli, from which they receive both urine and blood-supply. Recently Clarke, Evans, MacIntyre, and Milne (1955) have suggested that impaired excretion of ammonium in experimental salt depletion is the result of reduced renal plasma-flow, and consequent reduction in the tubular supply of glutamine and amino-acid substrate for synthesis of ammonium; this interesting hypothesis could equally well be invoked to explain our findings in renal disease. Alternatively, a reduction in glomerular filtration from disease might directly limit the excretion of ammonium by reducing the number of functioning nephrons.

The excretion of acid in different forms of renal disease

1. *General renal failure.* Over 40 years ago Henderson and Palmer (1915) found that most patients with 'chronic nephritis' could excrete a highly acid urine, but that their excretion of ammonium was markedly reduced. Our findings in patients with generalized forms of renal disease (glomerulonephritis, pyelonephritis, and malignant hypertension), and recent studies by Merrill (1955) and Giovannetti and Bigalli (1956), are in agreement with these early observations. We also found that the excretion of titratable acid was significantly reduced, owing to a fall in the excretion of phosphate buffer.

2. *Renal tubular acidosis.* Albright described this condition as a form of 'tubular-insufficiency-without-glomerular-insufficiency' in which the tubules are unable to excrete ammonium and an acid urine normally. He did not determine the glomerular filtration rate in most of his patients; since then, whenever this rate has been measured, it has been found to be reduced (Burnett, Burrows, and Commons, 1948; Pines and Mudge, 1951; Brooks, McSwiney, Prunty, and Wood, 1957; Reynolds, 1958; and the present study). The reduction, to between 15 and 50 per cent. of normal in our cases, is not gross, but is sufficient to explain the poor excretion of ammonium; and there is no need to suppose a specific tubular abnormality in this function (Fig. 15). The constant and characteristic tubular defect is inability to excrete a highly acid urine. In our patients the minimum urinary pH ranged from 5·7 to 7·0. This implies that the renal tubules were unable to excrete hydrogen ion against a urine:plasma concentration ratio greater than 2·5:1 to 50:1, whereas the normal kidney can achieve a ratio of 125:1 to 800:1. As a result of this tubular fault the excretion of titratable acid is reduced; urines more alkaline than

pH 6·0 also contain appreciable amounts of bicarbonate. But there is no absolute limitation in the excretion of titratable acid *per se*, for these patients can excrete normal amounts if presented with sufficient phosphate buffer (Figs. 8 and 12; Smith and Schreiner, 1954; Kaye, 1955; Reynolds, 1958; Frick, Rubini, aud Meroney, 1958).

Under the title 'incomplete syndrome of renal tubular acidosis' we have described three patients with generalized nephrocalcinosis who were unable to excrete a highly acid urine, but had no acidosis. These patients could excrete ammonium normally, which appears to explain their lack of acidosis. Their glomerular filtration rates were higher than those of patients with the 'complete' syndrome, and this in turn seems the likely explanation of their efficient excretion of ammonium.

Nephrocalcinosis is a very common feature of renal tubular acidosis; it was described in 44 of the 60 case reports (73 per cent.) which are known to us, and was present in nine out of 11 (82 per cent.) of our own patients with the 'complete' syndrome. Albright, Burnett, Parson, Reifenstein, and Roos (1946) ascribed it to a hypercalcuria resulting from chronic acidosis, and this explanation has gained wide acceptance. But there is a great deal of evidence suggesting that nephrocalcinosis is more intimately connected with the tubular lesion, and can arise without intervention of either acidosis or hypercalcuria:

(1) Nephrocalcinosis was present in our three patients with the 'incomplete' syndrome, who had the same defect in urinary acidification as patients with the classical syndrome, but neither acidosis nor hypercalcuria.

(2) A long history of renal calculi or nephrocalcinosis may precede symptoms attributable to acidosis. Subject 30, for example, passed a renal calculus at the age of 16, and was discovered to have generalized nephrocalcinosis 10 years later; yet the diagnosis of tubular acidosis was only made at the age of 40, some 24 years after his first urinary symptoms, and even then his acidosis was slight (plasma total CO_2 22·8 m-moles per litre). Subject 35 experienced repeated attacks of renal colic, with the passage of stones, for 37 years before he developed a crippling osteomalacia, which led to a correct diagnosis at the age of 59. These two histories suggest that renal calcification may precede acidosis by many years.

(3) Nephrocalcinosis and renal calculi have frequently been found in relatives of patients with renal tubular acidosis. Fig. 16 shows family trees with this feature; two of our own patients (Subjects 27 and 35) had relatives with renal disease, probably renal calculi, but we were unable to study these relatives. It seems likely that such persons, with calculi and nephrocalcinosis but no acidosis, have the same functional tubular abnormality as their less fortunate relatives with acidosis—inability to excrete highly acid urine.

How can nephrocalcinosis arising in these circumstances be explained? It has sometimes been suggested that persistent urinary alkalinity, or a reduced acidity, may be responsible (Fourman and McCance, 1955), for calcium salts are well known to be relatively insoluble in alkaline media. Harrison and Harrison (1955), from studies on acetazolamide-induced nephrocalcinosis in the rat, and findings on one patient with tubular acidosis (Harrison, 1954), have

suggested that reduced excretion of citrate may also be an important factor. Normally citrate, which forms a soluble and undissociated calcium complex, is excreted in increased amounts in alkaline urines, and it may then play a role in preventing the precipitation of calcium salts which might otherwise occur. Recent work by Evans, MacIntyre, MacPherson, and Milne (1957) suggests that excretion of citrate is determined, not by urinary pH, but by systemic acid-base balance, and in particular by intracellular pH, being increased by alkalosis and reduced by acidosis. Renal tubular acidosis is one of the few conditions in

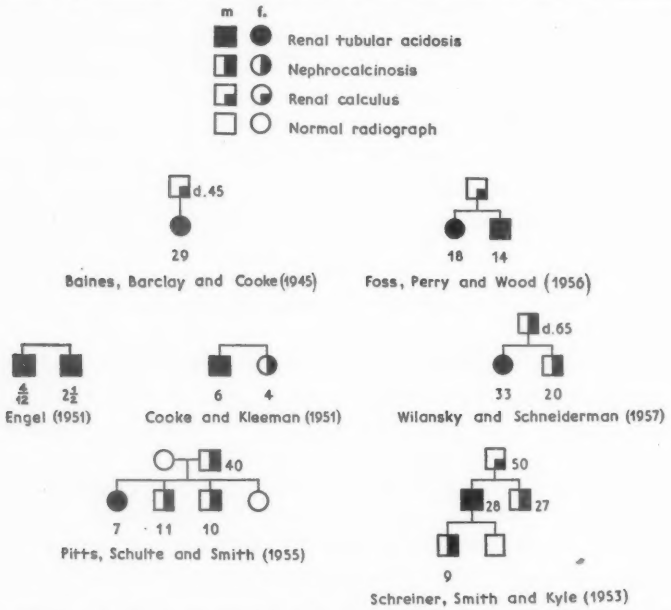


FIG. 16. Family trees of some reported patients with renal tubular acidosis. The age in years at the time of diagnosis or death is indicated wherever possible.

which an alkaline urine is excreted despite a systemic acidosis, and nephrocalcinosis might be expected to develop because of a low concentration of citrate in such a urine. We have studied the excretion of citrate in only two patients: Subject 30 with the complete syndrome and a mild acidosis, and Subject 38 with the incomplete syndrome (Appendix II). In keeping with the above hypothesis, the excretion of citrate was low for the urinary pH in both cases, particularly so in the patient who had an extracellular acidosis. Similar findings have recently been reported by Frick, Rubini, and Meroney (1958) and Bauld, MacDonald, and Hill (1958).

Evidence suggesting that renal tubular acidosis is sometimes a hereditary disorder has already been discussed. Fig 16 shows all the reported family trees of patients with tubular acidosis whose relatives have suffered from tubular acidosis, nephrocalcinosis, or renal calculi. The real incidence may be much higher, for few authors have mentioned the families of their patients, and only

two radiological surveys of families have been made (Schreiner, Smith, and Kyle, 1953; Pitts, Schulte, and Smith, 1955). In addition, three cases of tubular acidosis have been children of first-cousin marriages (Zweymuller and Rossler, 1954; Jurow and Warthen, 1955; and our own Subject 27). Altogether, hereditary transmission might be suspected in 11 out of 60 previously reported cases and two of our nine hitherto unreported cases of the complete syndrome, a total incidence of 19 per cent.; but information is not sufficient to decide on the usual mode of inheritance.

We envisage the natural history of renal tubular acidosis as follows. The essential tubular abnormality is inability to excrete a urine of low pH, a fault which may be either inherited or acquired. If renal function is otherwise intact, the subject will excrete sufficient ammonium to prevent severe acidosis; but he is liable to develop nephrocalcinosis and renal calculi. If infection, nephrocalcinosis, or urinary obstruction cause sufficient destruction of renal tissue, the patient will lose his ability to excrete ammonium, and acidosis will result. The frequent occurrence of potassium depletion and osteomalacia in tubular acidosis still requires explanation. Acidosis, which increases the excretion of both potassium and calcium, has been held responsible (Albright, Burnett, Parson, Reifenstein, and Roos, 1946), but this has never been proved by controlled observation. Excessive urinary loss of potassium in one potassium-depleted patient of the present series (Subject 33) persisted in spite of correction of the extracellular acidosis with alkaline sodium salts (Stanbury, 1958). If the segment of renal tubule which secretes hydrogen ion is the same as that which secretes potassium (Berliner, Kennedy, and Orloff, 1951), it is conceivable that a defect of this segment might cause excessive excretion of potassium even in the absence of acidosis. Bartter (1956) has also suggested that sodium depletion, and a consequent hyperaldosteronism, might cause the renal loss of potassium in this syndrome, but this was found not to be the case in Subject 33 (Stanbury, 1958). Nor it is certain that acidosis is the chief cause of the frequent osteomalacia; Stanbury (1957 *a*, 1957 *b*) has recently pointed out that a similar osteomalacia may complicate many different forms of renal disease when associated with increased resistance to the action of vitamin D, and that healing of osteomalacia in tubular acidosis has been reported only when vitamin D has been given in addition to alkalis.

3. *The kidney in potassium deficiency.* Clarke, Evans, MacIntyre, and Milne (1955) have shown that experimental deficiency of potassium in man is associated with inability to excrete urine of normal maximum acidity; by contrast, excretion of ammonium is well maintained. Our three patients were more severely depleted, and their limitation of urinary pH more marked. We also found that ammonium excretion was unaffected, or even increased, and we attribute this to the good overall renal function of these patients. Defective urinary acidification, however, is not a constant feature of potassium depletion, and is not very impressive when it does occur. Stanbury (1958) has studied a patient in whom potassium depletion, the result of chronic diarrhoea, was as severe as that found in any of the three subjects described here; his patient

could excrete urine of pH 5·1 while alkalotic. The figures of urinary pH during acidosis and potassium depletion found by Clarke, Evans, MacIntyre, and Milne (1955) (5·2 to 5·6) overlap with the figures of Pitts from subjects with a comparable acute acidosis and no potassium depletion (pH 4·49 to 5·34), and also with our own figures during a milder acidosis (pH 4·60 to 5·24). The potassium-depleted patients studied in the present work had a more marked impairment of urinary acidification, but only in the case of Subject 53 (steatorrhoea), who excreted the most acid urine of the three (pH 5·52), could this be ascribed with any confidence to potassium depletion. Subject 51 had potassium-losing renal disease and spotty nephrocalcinosis; following the argument used above, her inability to excrete a highly acid urine might be attributed to the tubular lesion that caused excessive potassium excretion. She could then be described as having 'the incomplete syndrome of renal tubular acidosis presenting potassium depletion'. Unfortunately we have not been able to study this patient since her deficiency was corrected, to see whether the defect in urinary acidification persists. Subject 52 had hyperaldosteronism and unilateral renal disease. His subsequent response to subtotal adrenalectomy and removal of a non-excreting kidney suggests that aldosterone itself may have determined the abnormal renal response to ammonium chloride (minimum pH 6·19); for, immediately after the operation and before any potassium was retained, the urinary pH fell to 5·39 for the first time (Wrong and Gowenlock, 1959). Eales and Linder (1956) and Milne, Muehrcke, and Aird (1957) have made similar observations on three patients with hyperaldosteronism due to adrenal adenoma. Perhaps aldosterone acts on the site in the renal tubule at which potassium and hydrogen ion compete for secretion (Berliner, Kennedy, and Orloff, 1951), forcing excretion of potassium at the expense of hydrogen ion, but it is difficult to reconcile this theory with the observed increase of ammonium excretion in these patients.

4. *The Fanconi sydrome.* Systemic acidosis is a common feature of the heterogeneous group of conditions constituting the Fanconi syndrome. From our limited experience of two cases, and a survey of the pertinent literature, we believe that this acidosis arises from the following abnormalities:

(1) Impaired excretion of ammonium (Subject 68 of this series; cases reported by Linder, Bull, and Grayce, 1949; Bickel and Hickmans, 1952; Bickel, Smallwood, Smellie, and Hickmans, 1952; Sirota and Hamerman, 1954; Tegelaers and Tiddens, 1955; Saville, Nassim, Stevenson, Mulligan, and Carey, 1955; Stanbury and Macaulay, 1957; and Case I of Kyle and Canary, 1956). These patients all had reduced glomerular filtration rates, often with azotaemia, and their inability to excrete ammonium cannot be regarded as a specific tubular fault. To our knowledge, only one patient (Case II of Kyle and Canary) has been reported with reduced excretion of ammonium and a normal filtration rate, the latter depending on a single determination of the creatinine clearance.

(2) Inability to excrete highly acid urine (Subject 63; and cases reported by Bickel, Smallwood, Smellie, and Hickmans, 1952; Milne, Stanbury, and Thomson, 1952; Jackson and Linder, 1953; Sirota and Hamerman, 1954;

Tegelaers and Tiddens, 1955; Kyle and Canary, 1956; Stanbury and Macaulay, 1957; and Hooft and Vermassen, 1958). Every one of the patients referred to had hypokalaemia, often with clinical evidence of potassium depletion. The observed defect in urinary acidification has frequently been more marked than that found by us in potassium depletion alone; for instance, the patient described by Milne, Stanbury, and Thomson passed urine of pH 6·7 to 7·2 when her serum-potassium concentration was 2·2 m-equiv. per litre and total CO_2 14 m-moles per litre. But potassium depletion might conceivably be responsible, and the defect cannot be regarded with certainty as one of the primary tubular faults of the syndrome. By contrast, the same defect in renal tubular acidosis has been amply shown to be independent of the state of body potassium.

(3) Excretion of organic anion. Many organic acids of physiological importance are moderately strong acids, with pK values near or below the minimum urinary pH, and cannot therefore be excreted as free acids but must exist in the urine mainly as salts. Lactic acid, for example, has a pK of 3·85, and is at least 85 per cent. in the form of lactate in even the most acid urines. Some other organic acids of low pK value are acetic (pK 4·7), acetoacetic (3·8), and β-hydroxybutyric acid (4·7), and the dicarboxylic amino acids, glutamic (pK_1 2·2) and aspartic acid (pK_1 1·9). The excretion of organic anions as salts constitutes a drain of potential alkali from the body, for normally these anions are metabolized ultimately to bicarbonate or hydroxyl ion (which accounts for the well-known alkalinizing effects of citrate, acetate, and lactate salts, for example). Urinary loss of organic anion is seldom gross enough to affect acid-base balance appreciably, but it may help to account for an otherwise inexplicable acidosis in a few patients with the Fanconi syndrome. McCune, Mason, and Clarke (1943) described severe acidosis in a boy aged nine years, who was able to excrete urine of pH 4·8 and large amounts of ammonium. His urine contained 60 to 260 m-equiv. of organic 'acid' a day, of which at least 32 per cent. was organic anion of low pK value—lactate, β-hydroxybutyrate, and dicarboxylic amino-acid anion. Excretion of organic anion may also have contributed to the acidosis of patients described by Jackson and Linder (1953), and Salassa, Ulrich, and Hayes (1954). A patient reported by Dawson, Dempsey, Bartter, Leaf, and Albright (1953) might also be included here: although described as a case of 'renal tubular acidosis', she was able to excrete urine of pH 4·5 with fair amounts of ammonium, had a renal glycosuria, and excreted up to 150 m-equiv. of unidentified 'acid' (anion) in the urine daily.

An 'organic acidaemia' has been regarded as another possible cause of acidosis (Bickel and Hickmans, 1952), but has not been unequivocally demonstrated. The above list may not exhaust the possibilities, but it will satisfactorily account for all cases of acidosis in the Fanconi syndrome so far reported.

We are grateful to the many physicians and surgeons who allowed us to study patients under their care and thereby made this investigation possible. Particular thanks are due to Dr. S. W. Stanbury for invaluable advice, and to

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APPENDIX I

Chemical methods. The following analytical procedures were used for plasma and urinary constituents: Ammonium and urea, the microdiffusion method of Conway (1947); bicarbonate, the method of Van Slyke and Neill (1924) for total CO_2, and calculation using the Henderson–Hasselbalch equation; creatinine, the method of Bonsnes and Taussky (1945) for urine, and of Roscoe (1953) for plasma; inorganic phosphorus, the method of Fiske and Subbarow (1925); sodium and potassium, flame photometry; calcium, the method of Clark and Collip (1925); chloride, the method of Sanderson (1952); and citrate, the method of McCardle (1955). All determinations of ammonium, urea, creatinine, phosphorus, calcium, and citrate, were made in duplicate. Specimens of urine which could not be analysed for ammonium immediately were preserved by freezing or the addition of concentrated sulphuric acid. Urinary osmolarity was taken as $2(Na+K+NH_4)+$urea.

Urinary pH was determined with a glass-electrode pH-meter at room temperature (18° to 23° C); titratable acidity (T.A.) by titrating a sample to pH 7·4 with N/20 sodium hydroxide. With urine containing appreciable amounts of bicarbonate (that is, over pH 6·0) calculation of hydrogen ion excretion as (NH_4+T.A. $-HCO_3$) results in significant error, for the titratable acidity depends partly on bicarbonate and dissolved CO_2, and variable amounts of the latter may be lost by diffusion. With such specimens we have followed the procedure recommended by Albright and Reifenstein (1948) for determination of (T.A. $-HCO_3$): a standard excess of acid is added, and the specimen is evacuated with a water-pump to drive off CO_2, and back-titrated to pH 7·4. When (T.A. $-HCO_3$) is determined in this way, specimens more alkaline than pH 6·6 to 6·8 have a negative value because of their high concentration of bicarbonate.

Calculations. Our results have not been corrected for body weight or surface area. Many of our subjects, especially those with renal tubular acidosis, were dwarfed or wasted as a result of their disease, and such adjustment would give a falsely inflated index of their renal function. This difficulty was well illustrated by a dwarfed and rachitic patient with the adult Fanconi syndrome studied by Anderson, Miller, and Kenny (1952); the absolute indices of renal function were almost doubled when adjusted for a surface area of 1·73 square metres, yielding a corrected urea clearance of 174 per cent., and a maximum tubular reabsorptive capacity for glucose of 212 per cent. of normal. Ideally, a patient's response to a standardized acidotic stress would be corrected by body weight or surface area *in the healthy state*, but this information is seldom available, and we have preferred to make no correction at all.

The contributions of phosphate and creatinine to titratable acid (Fig. 2) have been calculated from the known pH of the urine, its titratable acidity, and the Henderson–Hasselbalch equation, assuming pK values of 6·85 and 4·97 respectively. (These figures have been checked by the determination of pK′ in solutions of ionic strengths corresponding to dilute and concentrated urines, and in no case did the pK′ value differ by more than 0·12 from the assumed figure.) A

few patients (Subjects 7, 11, 18, 19, and 31) showed by wide hour-to-hour variations in the excretion of all urinary constituents that they were unable to empty their bladders consistently. In such cases a correction has been made by assuming that renal excretion of creatinine was constant over the period of study. This correction has no effect on the six-hour rates of excretion shown in the Tables. The urea clearance has been expressed as a percentage of 54 ml. per minute ('standard' clearance) or 75 ml. per minute ('maximum' clearance), as suggested by Moller, McIntosh, and Van Slyke (1929), but without correction for surface area.

APPENDIX II

Case Reports

Subjects with renal tubular acidosis

Subject 27, D. S., a boy aged 14 years (Professor C. E. Dent's patient). The renal lesion may be hereditary in this case; his parents are first cousins, and a paternal uncle is said to have kidney and bone disease. At the age of four years his parents noticed excessive thirst and polyuria. In the next few years he grew very slowly, and by the age of nine had obvious knock-knees, which were painful and made running impossible. X-rays at this time revealed rachitic changes at the knees and ankles. The serum calcium was 9·7 mg. per 100 ml., inorganic phosphorus 2·8 mg. per 100 ml., alkaline phosphatase 25 King–Armstrong units per 100 ml., and blood urea 45 mg. per 100 ml. An intravenous pyelogram showed poor concentration of dye and bilateral nephrocalcinosis. Treatment with calciferol and sodium citrate was followed by rapid symptomatic improvement and disappearance of radiological evidence of rickets. In 1956, aged 13, he again complained of pain in the knees, and was admitted to University College Hospital for investigation. Examination showed an under-sized boy with genu valgum. His urine, which contained a trace of protein but no sugar, had a fixed specific gravity (1,008 to 1,011 after overnight dehydration), and showed a normal amino-acid pattern on chromatography. There was no radiological or biochemical evidence of active rickets, and his blood urea was 34 to 40 mg. per 100 ml. When alkali treatment was stopped, his plasma CO_2 fell from 23·9 to 17·8 m-moles per litre, but the pH of his urine did not fall below 6·8.

Subject 28, S. B., a woman aged 25. This patient was originally described by Milne, Stanbury, and Thomson in 1952 (their Case 2). The first symptoms of her disease were repeated attacks of flaccid paralysis, almost certainly the result of potassium depletion, at the age of nine years. These attacks were thought to be due to familial periodic paralysis, and were treated fairly successfully with potassium chloride. At the age of 18 she developed aching pains in the chest, thighs, and back, and X-rays showed generalized osteomalacia and nephrocalcinosis. She had a hyperchloraemic acidosis (plasma CO_2 16·9 m-moles per litre), and her urine was neutral to litmus. Chromatography of the urine showed no abnormal amino acids. Treatment with calciferol and alkalis was followed by rapid healing of the bones. Apart from occasional attacks of urinary infection, she has since remained well, and has married and successfully undergone a pregnancy. Although her renal tubular abnormality remains (Table V), she has not required treatment with alkalis for the past 18 months.

Subject 29, F. G., a man aged 39 (Dr. A. R. Harrison's patient). At the age of 24 he developed dyspeptic symptoms, and six years later suffered a perforated peptic ulcer. Although he has taken antacids for years, he has relied mainly on

aluminium hydroxide, and has never used sodium bicarbonate. In 1954, aged 36, he had a sudden attack of right-sided renal colic and haematuria, and X-rays showed bilateral renal calculi. A left partial nephrectomy for stone was subsequently carried out, but urinary symptoms persisted, and he occasionally passed small urinary calculi. In 1957, aged 39, he was admitted to St. Philip's Hospital, London. Additional complaints were recent loss of weight, extreme fatigue, and paraesthesiae of the hands and face. Physical examination showed a rather thin man, with a blood-pressure of 110/80. His urine contained a trace of protein and a few pus-cells, but was repeatedly sterile on culture. X-rays showed very small areas of calcification throughout both kidneys; there was no evidence of osteomalacia. Serum analysis (Table V) showed a hyperchloraemic acidosis and a rather low serum-potassium level, but no significant azotaemia.

Subject 30, W. M., a man aged 40. He first had an attack of right-sided renal colic at the age of 16 years. Ten years later symptoms returned, and X-rays showed marked generalized nephrocalcinosis. During the next 14 years he had numerous attacks of pain on both sides, and frequently passed small urinary calculi. In 1955, at the age of 40, his blood-pressure was found to be 215/145, and he was admitted for investigation. He was small in build, but well-proportioned. The fundi showed early hypertensive retinitis. The urine contained a trace of protein, but no sugar. While taking a normal ward diet his urine contained 300 mg. of calcium in 24 hours. X-rays confirmed the presence of nephrocalcinosis (Plate 19, Fig. 17), which had altered little in 14 years. There was a very mild acidosis (plasma total CO_2 22·8 m-moles per litre) and a rather low plasma-potassium concentration (2·8 to 3·9 m-equiv. per litre), but his blood urea was normal. Excretion of citrate was 38 and 41 mg. in 24 hours. Treatment with alkali (80 m-equiv. of potassium citrate daily) relieved the acidosis, and reduced urinary excretion of calcium to 190 mg. daily. Hypertension was easily controlled with reserpine and pentolinium, and his blood-pressure since that time has varied about 150/100. Recently alkali treatment was stopped, but after one month he was noticeably hyperpnoeic (plasma total CO_2 19·6 m-moles per litre; plasma potassium 3·6 m-equiv. per litre), and treatment was resumed.

Subject 31, E. L., a man aged 42 (Professor C. E. Dent's patient). For as long as he could remember he had suffered from excessive thirst and urinary frequency, with nocturia. At the age of 32, while serving in the tropics, he had a short episode of diarrhoea and fever. While recovering, he had an attack of severe generalized weakness, with paralysis of the limbs and absent tendon reflexes. Shortly afterwards he developed renal colic, and X-rays showed bilateral renal calculi. During the next few years he passed many small stones in his urine. At the age of 35 he developed severe girdle pains around the lower ribs, made worse by coughing. He became very weak, and was admitted to University College Hospital for investigation. Here he was found to have radiological osteomalacia, a hyperchloraemic acidosis (plasma chloride 109 m-equiv. per litre; total CO_2 18·3 m-moles per litre), and a low serum-potassium concentration (3·1 m-equiv. per litre). His urine contained a trace of protein and numerous pus-cells, but was repeatedly sterile on culture; the maximum specific gravity after deprivation of fluid was 1,014. After treatment with calciferol and alkalis his symptoms rapidly disappeared. Since 1954 his only treatment has been sodium bicarbonate by mouth. He still has occasional urinary symptoms, but is passing stones less frequently.

Subject 32, A. B., a woman aged 48. She was said to have had rickets as a child, and was always smaller than her brothers and sisters. There was no family

history of renal disease. At the age of 28, and again at 36, she suffered attacks of pyelitis, and after the second attack an intravenous pyelogram showed a left renal calculus, which was removed at operation shortly afterwards. Two years later, aged 39, she first noticed pains in the buttocks, spine, and thighs, and in the next four years these became increasingly severe, eventually confining her to bed. At the same time she lost height, and developed a hunchback and bow legs. In 1951, aged 43, she was readmitted to hospital. She was a very small woman, only 4 ft. 2½ in. (128 cm.) in height, with severe thoracic kyphoscoliosis and bowed tibiae. The blood-pressure was 120/80. X-rays showed a generalized decrease in bone density, with pseudo-fractures of ribs, pelvis, and one tibia and fibula, and small patches of calcification throughout both kidneys. The urine contained a trace of protein, but no sugar, and was constantly alkaline (pH 6·8 to 7·5 even after 3 g. of ammonium chloride); specific gravity 1,010 to 1,014. The excretion of amino acids was normal, 135 mg. (as N) in 24 hours, with a normal chromatographic pattern. Analysis of serum showed a chemical osteomalacia and mild acidosis (total CO_2 19·8 m-moles per litre). After treatment with calciferol (150,000 units daily) and alkalis (sodium and potassium citrate) her bone pain rapidly disappeared. Five months later a bilateral tibial osteotomy was performed to correct her bow legs, and within five weeks she was beginning to walk again. Since then she has steadily improved. Treatment with calciferol was stopped after two years, when her serum calcium had increased to 12·4 mg. per 100 ml., but she continues to take alkalis. There has been no further deterioration in renal function; when she was last seen her blood urea was 42 mg. per 100 ml., and she was free of symptoms.

Subject 33, I. B., a woman aged 51. This patient, an epileptic since the age of 28, had also suffered from recurrent allergic purpura for 11 years. She was admitted to hospital because of frequent vomiting, symptoms of tetany, recent loss of weight, physical weakness, and the finding of a low serum-potassium concentration. She had no definite urinary symptoms. Physical examination showed a small woman, only 4 ft. 8 in. (142 cm.) in height. Trousseau's sign was positive. Her blood-pressure was 120/60, and her heart was enlarged, but without murmurs. The urine contained a trace of albumin, but no glucose, and the total excretion of amino acids was within normal limits. Plasma analysis showed a hyperchloraemic acidosis (Table V), potassium 2·4 m-equiv. per litre, urea 44 mg. per 100 ml., calcium 10·4 mg. per 100 ml., phosphorus 3·1 mg. per 100 ml., and alkaline phosphatase 10 King–Armstrong units per 100 ml. X-rays revealed bowing of both femora suggestive of former rickets, but no sign of active bone disease; there was no radiological evidence of nephrocalcinosis. After administration of ammonium chloride the urinary pH fell only to 6·83.

Subject 34, J. C., a woman aged 52, for two years had suffered attacks of pain in the left loin, dysuria, and urinary frequency. She had become very thirsty, had passed one small calculus, and had aching pains in her back and legs. She was tender in the left loin. The blood-pressure was 130/80. Her urine contained a few pus-cells, but no protein, and was sterile on culture (maximum specific gravity 1,010; 405 m-osmoles per litre). Her plasma potassium was 3·0 m-equiv. per litre, total CO_2 21·4 m-moles per litre, chloride 113 m-equiv. per litre, calcium 9·7 mg. per 100 ml., phosphorus 3·0 mg. per 100 ml., alkaline phosphatase 7·2 King–Armstrong units per 100 ml., and urea 43 mg. per 100 ml. The serum albumin was 3·5 g. per 100 ml., and globulin 4·7 g. per 100 ml.; electrophoresis showed a marked increase in the gamma-globulin fraction. The Mantoux

(1/1,000) and Kveim reactions were negative. The skeleton was radiologically normal, but both kidneys showed calcification of the medullary pyramids. On a low-calcium diet her excretion of calcium was 130 mg. daily. Sodium bicarbonate, 14 g. daily, increased the plasma total CO_2 to 24 m-moles per litre, but did not relieve her thirst. In an attempt to reduce her nephrocalcinosis she was given a course of intravenous sodium ethylenediamine tetra-acetic acid ('versene'), as recommended by Clarke, Clarke, and Mosher (1955), to a total of 76 g.; but, although the excretion of calcium increased to 250–540 mg. daily, there was no improvement in renal function or calcification.

Subject 35, J. C., a man aged 60 (Dr. S. Oleesky's patient). His father was said to have died of 'Bright's disease', and had frequently had haematuria; one brother has had a kidney removed, probably for stone. The patient was always smaller than his five brothers and sisters. About the age of 18 years he had an attack of right renal colic, and this recurred about once a year for the next 30 years, frequently with accompanying haematuria. At the age of 55 he first noticed pain in the back and neck, and found that he was limping; he became thirsty, and had to get up two or three times at night to pass urine. Generalized aches and pains made it increasingly difficult to walk; he lost height, and his tailor noticed that his trunk was shorter. In 1955, aged 59, he was admitted to hospital. He was a small man, only 4 ft. 10 in. (147 cm.) in height; he remembered being six inches taller as a young man. His ribs were tender, and he had a marked thoracic kyphosis. The blood-pressure was 130/85. X-rays showed demineralized bones, with pseudo-fractures of ribs, pelvis, and femora, and diffuse nephrocalcinosis with a right ureteric calculus. The urine contained a trace of protein, but no sugar; the specific gravity after pitressin was 1,010. A 24-hour specimen of urine contained 187 mg. of amino-acid nitrogen, a normal amount. Cultures of urine showed no growth. The serum chloride was 120 m-equiv. per litre, total CO_2 16 m-moles per litre, potassium 3·8 m-equiv. per litre, and blood urea 23 to 62 mg. per 100 ml. He was treated with alkalis and calciferol, and rapidly lost his symptoms. He has since remained well, except for occasional dysuria and urinary frequency.

Subject 36, E. B., a woman aged 42, the subject of an earlier report by Fitzgerald and Fourman (1955). At the age of 38 she was admitted to hospital with a story of thirst, polyuria, and increasing weakness leading to paralysis. She had passed a calculus five years previously. Her serum potassium was 1·8 m-equiv. per litre, total CO_2 14 m-moles per litre, and urinary pH 6·5. There was no abnormal aminoaciduria or organic aciduria. Since that time she has taken a sodium and potassium bicarbonate mixture, and has remained well. Recent X-rays show small intrarenal calcifications on both sides.

Subject 37, M. J., a woman aged 44. Six months before the present study she became weak and thirsty, and was admitted to hospital almost completely paralysed, with flaccid limbs and absent tendon reflexes. She was vomiting bile-stained fluid, and bowel sounds were absent. The blood-pressure was 70/50. The plasma potassium was 1·9 m-equiv. per litre, chloride 113 m-equiv. per litre, and total CO_2 11 m-moles per litre. With potassium repletion her condition improved, but she suffered attacks of tetany after the second day of treatment (serum calcium 8·0 mg. per 100 ml., phosphorus 4·8 mg. per 100 ml., alkaline phosphatase 7 King–Armstrong units per 100 ml.). She has since had several attacks of tetany a month, although the serum-electrolyte levels, whenever measured, have been within normal limits. The urine (maximum specific

gravity 1,018; 620 m-osmoles per litre) contains no albumin, and has no deposit. There is no aminoaciduria or excessive excretion of organic acids. X-rays reveal no nephrocalcinosis or evidence of bone disease.

Incomplete syndrome of renal tubular acidosis (nephrocalcinosis and inability to excrete acid urine, without systemic acidosis)

Subject 38, R. M., a man aged 44. In 1942, aged 31, this patient was struck in the perineum by an iron bar. His right testis became swollen and tender, and a week later he developed profuse haematuria and severe intermittent pain in the left renal angle. Micturition was painful and difficult. After a further week he was admitted to hospital. There was tenderness in the left renal angle, the right testis was swollen and hard, and his urine contained bright red blood. Cystoscopy showed evidence of cystitis. Intravenous pyelography and a right retrograde pyelogram (performed because this side had not shown well in the excretory pyelogram) were normal. Subsequently his symptoms disappeared, and he was sent home. During the succeeding years he remained well, and free from urinary symptoms. In March 1955, 13 years after his original illness, he suddenly developed painless haematuria, which lasted for four days, and for this reason was admitted to hospital. Examination showed a very healthy-looking man with a blood-pressure of 120/80, and no evidence of the old perineal injury. His urine contained a trace of protein and a moderate number of pus-cells, but was three times sterile on culture. X-rays (Plate 19, Fig. 18) showed marked generalized nephrocalcinosis; an intravenous pyelogram revealed that the whole calyceal system on both sides was slightly dilated, and that each minor calyx was capped by a small cluster of intrarenal calcifications. There was no evidence of bone disease. Plasma chemistry showed no abnormalities (urea 34 mg. per 100 ml., total CO_2 28·4 m-moles per litre, chloride 103 m-equiv. per litre, potassium 4·2 m-equiv. per litre, sodium 141 m-equiv. per litre, calcium 10·6 mg. per 100 ml., inorganic phosphorus 4·5 mg. per 100 ml., alkaline phosphatase 6·5 King–Armstrong units per 100 ml., albumin 4·0 g. and globulin 3·6 g. per 100 ml.). The endogenous creatinine clearance was 98 ml. and inulin clearance 102 ml. per minute. While he was receiving a normal ward diet his average daily excretion of calcium over a three-day period was 140 mg. After 24 hours without fluids the concentration of his urine was virtually isotonic (328 m-osmoles per litre). His urine was persistently alkaline or only slightly acid (pH 6·7 to 7·1), but contained unusually large amounts of ammonium for this reaction (Fig. 11). With ammonium chloride in the usual dosage, the lowest urinary pH was 6·42. This dose was twice repeated within the next 24 hours (23 g. of ammonium chloride in all), producing a moderate acidosis (plasma total CO_2 19·4 m-moles per litre); there was no further drop in urinary pH, but the excretion of ammonium rose to 96 μ-equiv. per minute. Five days later he was found to have corrected this acidosis (plasma total CO_2 25·9 m-moles per litre). Ammonium chloride in the initial dosage was then given during intravenous infusion of isotonic sodium phosphate solution of pH 7·4. The urinary pH fell a little further than previously, the lowest reached being 5·86, and excretion of titratable acid rose to 106 μ-equiv. per minute (Fig. 12). During phosphate infusion the rate of excretion of ammonium was very high (up to 135 μ-equiv. per minute), which may have been partly the effect of the very large dose of ammonium chloride given five days earlier.

Although there was no clinical or biochemical evidence of potassium deficiency, it seemed important to exclude this as a cause of his abnormal response to ammonium chloride. Repeated determinations of the plasma-potassium

concentration, and an electrocardiogram, were normal. The total exchangeable potassium, estimated with the method described by Corsa, Olney, Steenberg, Ball, and Moore (1956) was 2,820 m-equiv., or 37·4 m-equiv. per kg., a normal figure by this method, although in the lower part of the normal range. The patient was thought to have an incomplete form of the syndrome of renal tubular acidosis, probably the result of a pyelonephritic process originating at the time of his perineal injury and subsequent instrumentation. Since this diagnosis was made he has been closely watched for two and half years as an out-patient. He has had no further symptoms, and has not developed acidosis; recent X-rays show that his nephrocalcinosis is no more extensive. Excretion of citrate on three widely separate days, while he was taking his usual diet, was 115 mg., 145 mg., and 450 mg.

Subject 39, L. E., a man aged 30 (Dr. A. R. Harrison's patient). About the age of 20 he noticed that he was needing to drink more than other people, and was getting up once or twice at night to pass urine. At the age of 30 he was found at a routine medical examination to have proteinuria, and X-rays showed small flecks of calcium scattered through both kidneys (Plate 20, Fig. 19). Physical examination revealed no abnormality. The urine contained a number of red cells and leucocytes, but was twice sterile on culture. The highest specific gravity after 16 hours without fluids was 1,010. While taking a normal diet he excreted 230 mg. of calcium in his urine in 24 hours. X-rays of the long bones, hands, and skull showed no abnormality. Analysis of plasma showed no biochemical abnormalities (urea 22 mg. per 100 ml., total CO_2 27·7 m-moles per litre, potassium 4·1 m-equiv. per litre, calcium 10·6 mg. per 100 ml., phosphorus 3·2 mg. per 100 ml., alkaline phosphatase 7·5 King–Armstrong units per 100 ml.). The endogenous creatinine clearance was 53 ml. per minute, and the 'maximum' urea clearance 50 ml. per minute (66 per cent. of normal). He was given ammonium chloride on two occasions, separated by over a week. The results were identical—inability to excrete urine of normal minimum pH, but good excretion of ammonium (Table VI; Fig. 10).

Subject 40, L. K., a man aged 39 (Professor C. E. Dent's patient). At the age of 24 he had an attack of severe colicky pain in the mid-line of the lower abdomen. Thirteen years later he experienced a similar attack, accompanied by strangury and pain in the penis; X-rays showed bilateral nephrocalcinosis. Subsequently his lower abdominal pain frequently recurred, and was often associated with haematuria; there was occasional pain in the left loin, but he never passed a calculus. In 1957, aged 39, he entered University College Hospital. He was a healthy-looking man, with a blood-pressure of 140/95. The lower pole of the right kidney was tender, and the left testis atrophic as a result of an earlier mumps orchitis. The urine contained a trace of protein and a moderate number of pus-cells and red cells, but it was twice sterile on culture. Paper chromatography showed no abnormal aminoaciduria. After overnight deprivation of fluids his urine had a specific gravity of 1,011. With a normal diet his urine contained 110 mg. of calcium in 24 hours. Analysis of plasma showed no biochemical abnormalities (urea 36 mg. per 100 ml., total CO_2 28·9 m-moles per litre, potassium 4·5 m-equiv. per litre, calcium 10·1 mg. per 100 ml., phosphorus 3.6 mg. per 100 ml., alkaline phosphatase 4·5 King–Armstrong units per 100 ml.). The endogenous creatinine clearance was 79 ml. per minute, and the 'maximum' urea clearance 43 ml. per minute (57 per cent. of normal). He was given ammonium chloride on two occasions, with three days separating the tests. His urinary pH fell no further than 6·0; the excretion of ammonium was as great as in normal subjects on the first occasion (52 μ-equiv. per minute), and on

the second was increased above normal, perhaps as a result of the initial stimulus.

Severe potassium depletion

Subject 51, M. N., a woman aged 48. *? Potassium-losing renal disease.* She had suffered from repeated attacks of pain in the right loin, dysuria, and fever, for three years, culminating in an attack of generalized paresis, in which her serum potassium was 2·1 m-equiv. per litre. The blood-pressure was 95/60. There was spotty nephrocalcinosis on radiography, and diminished urinary excretion of calcium (30 to 80 mg. daily). The urine contained a trace of albumin, and pus-cells, but was sterile on culture. There was no acidosis. Excretion of aldosterone was slightly increased after repletion with potassium (38 μg. in 24 hours by the method of Ayres, Garrod, Simpson, and Tait, 1957; normal range 4 to 24 μg. in 24 hours).

Subject 52, A. R., a man aged 53. *Unilateral renal disease and hyperaldosteronism.* He had a six months' history of polyuria, thirst, weakness, and loss of weight. There was severe hypertension, a functionless right kidney, hypokalaemic alkalosis, and excessive urinary excretion of aldosterone (71 μg. in 24 hours). Small adrenals, normal in histological appearance, and an ischaemic right kidney, were found at operation. The patient is the subject of a separate report (Wrong and Gowenlock, in preparation).

Subject 53, A. P., a woman aged 58. *Idiopathic steatorrhoea.* She had had diarrhoea for 30 years and recent polyuria, with episodes of flaccid paralysis. The faecal fat was 40 per cent., and the glucose-tolerance curve was flat. The serum potassium was 1·9 m-equiv. per litre, the urinary potassium 7 m-equiv. per day, and faecal potassium (during a slight clinical remission) 22 m-equiv. per day. In spite of multiple absorption defects, this patient showed the usual blood changes after taking ammonium chloride.

Recovery from anuria

Subject 64, K. M., a woman aged 36. Anuria developed after an incompatible blood transfusion. She was treated conservatively, and diuresis started on the 15th day of anuria. Two days later she complained of paraesthesiae around the mouth, and the serum potassium, previously 3·3 to 3·9 m-equiv., was found to be 2·4 m-equiv. per litre. After oral and parenteral potassium she made an uninterrupted recovery. Her response to ammonium chloride was determined twice during recovery, on the 10th and 16th days of diuresis. In spite of the earlier episode of hypokalaemia, it is unlikely that she was significantly potassium-depleted on these two occasions; there were no suggestive symptoms, her serum concentration of potassium was normal, and a 24-hour measurement of exchangeable potassium, using the method of Aikawa, Harrell, and Eisenberg (1952), was 1,590 m-equiv., or 34·6 m-equiv. per kg., a normal figure, on the 15th day of diuresis.

Subject 65, A. D., a woman aged 32, was anuric for about 36 hours after an incomplete abortion. During the next five days she passed large quantities of urine, and became clinically dehydrated, with the blood urea 240 mg. per 100 ml. Her subsequent recovery was uneventful. Ammonium chloride was given 11 weeks after her episode of anuria; at this time she was still complaining of thirst and polyuria, but could concentrate her urine to 790 m-osmoles per litre after pitressin.

Subject 66, M. S., a man aged 52, suffered from severe hypotensive shock after an injection of 400,000 units of procaine penicillin, and subsequently had

almost complete anuria for 11 days. After recovery he was troubled by persistent thirst and polyuria. These symptoms were still present when he was given ammonium chloride 10 months later, and he was unable to excrete urine more concentrated than 365 m-osmoles per litre after pitressin or 16 hours without fluids.

Fanconi syndrome

Subject 67, a woman aged 47 (Dr. R. B. Evans's patient). For six years this patient had suffered from osteomalacia and recurring attacks of hypokalaemic paralysis. Her urine was free from protein and glucose, but contained excessive amounts of several amino acids, notably serine, threonine, glutamine, citrulline, and arginine. The specific gravity of the urine varied between 1,005 and 1,010; there was no acidosis or nephrocalcinosis. A detailed report appears elsewhere (Davies, Evans, Rees, and Fourman, 1958).

Subject 68, A. E., a man aged 65 (Dr. C. S. D. Don's patient). This man, who had multiple myelomatosis and Bence-Jones proteinuria, developed severe and progressive renal failure, from which he subsequently died. As an incidental finding he was noted to have renal glycosuria and a gross aminoaciduria (chiefly glycine, glutamic acid, valine, and leucine). The patient is the subject of a separate report (Short, 1959). An association of myelomatosis with renal glycosuria and aminoaciduria has been previously recorded by Sirota and Hamerman (1954), Dragsted and Hjorth (1956), and Engle and Wallis (1957).

Summary

A short test using ammonium chloride has been employed to assess the ability of the kidney to excrete ammonium and an acid urine. Ten normal subjects, and over 50 patients with different forms of renal disease, have been studied.

Patients with the classical syndrome of renal tubular acidosis were unable to excrete urine of normal minimum pH. The same impairment was found in severely potassium-depleted subjects, in some patients with persistent hypercalcaemia, and in one patient recovering from acute anuria. Most patients with severe general renal failure excreted urine as acid as those with normal renal function.

The rate of ammonium excretion after ammonium chloride was proportional to the glomerular filtration rate, and was invariably depressed in general renal failure. Reduced ammonium excretion was found in eight out of nine patients with renal tubular acidosis, but did not appear to be a specific abnormality of this syndrome, as glomerular filtration was correspondingly reduced.

We have studied three patients who have what appears to be an incomplete form of the syndrome of renal tubular acidosis. These patients had generalized nephrocalcinosis, and were unable to excrete urine of normal minimum pH, but they had no extracellular acidosis. All three had relatively normal glomerular filtration rates and high levels of ammonium excretion, which appeared to prevent them from developing acidosis.

The findings in two patients with the Fanconi syndrome suggest that the

acidosis frequently reported in this condition has multiple causes. One of our patients was severely depleted of potassium, and the other had advanced renal failure; their responses to ammonium chloride were characteristic of these two abnormalities.

REFERENCES

Aikawa, J. K., Harrell, G. T., and Eisenberg, B. (1952) *J. clin. Invest.* **31**, 367.

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A. (1946) *Medicine (Baltimore)*, **25**, 399.

—— Consolazio, W. V., Coombs, F. S., Sulkowitch, H. W., and Talbott, J. H. (1940) *Bull. Johns Hopk. Hosp.* **66**, 7.

—— and Reifenstein, E. C. (1948) *The Parathyroid Glands and Metabolic Bone Disease.* Baltimore.

Anderson, I. A., Miller, A., and Kenny, A. P. (1952) *Quart. J. Med.* N.S. **21**, 33.

Ayres, P. J., Garrod, O., Simpson, S. A., and Tait, J. F. (1957) *Biochem. J.* **65**, 639.

Baines, G. H., Barclay, J. A., and Cooke, W. T. (1945) *Quart. J. Med.* N.S. **14**, 113.

Bartter, F. C. (1956) *Metabolism*, **5**, 369.

Bauld, W. S., MacDonald, S. A., and Hill, M. C. (1958) *Brit. J. Urol.* **30**, 285.

Begun, A., and Munster, E. (1919) *Z. exp. Path. Ther.* **20**, 78.

Berliner, R. W. (1952) *Fed. Proc.* **11**, 695.

—— Kennedy, T. J., and Orloff, J. (1951) *Amer. J. Med.* **11**, 274.

Bickel, H., and Hickmans, E. M. (1952) *Acta paediat. (Uppsala)* **42**, Suppl. **90**, 137.

—— Smallwood, W. C., Smellie, J. M., and Hickmans, E. M. (1952) Ibid. **42**, Suppl. **90**, 27.

Bonsnes, R. W., and Taussky, H. H. (1945) *J. biol. Chem.* **158**, 581.

Brazeau, P., and Gilman, A. (1953) *Amer. J. Physiol.* **175**, 33.

Brooks, R. V., McSwiney, R. R., Prunty, F. T. G., and Wood, F. J. Y. (1957) *Amer. J. Med.* **22**, 391.

Buchanan, E. U., and Komrower, G. M. (1958) *Arch. Dis. Childh.* **33**, 532.

Burnett, C. H., Burrows, B. A., and Commons, R. R. (1948) *J. clin. Invest.* **27**, 527.

Butler, A. M., Wilson, J. L., and Farber, S. (1936) *J. Pediat.* **8**, 489.

Christensen, H. N. (1957) *Amer. J. Med.* **23**, 163.

Clark, E. P., and Collip, J. B. (1925) *J. biol. Chem.* **63**, 461.

Clarke, E., Evans, B. M., MacIntyre, I., and Milne, M. D. (1955) *Clin. Sci.* **14**, 421.

Clarke, N. E., Clarke, C. N., and Mosher, R. E. (1955) *Amer. J. med. Sci.* **229**, 142.

Cohen, S. I., Fitzgerald, M. G., Fourman, P., Griffiths, W. J., and de Wardener, H. E. (1957) *Quart. J. Med.* N.S. **26**, 423.

Conway, E. J. (1947) *Microdiffusion Analysis and Volumetric Error.* London.

Cooke, R. E., and Kleeman, C. R. (1951) *Yale J. Biol. Med.* **23**, 199.

Corsa, L., Olney, J. M., Steenberg, R. W., Ball, M. R., and Moore, F. D. (1950) *J. clin. Invest.* **29**, 1280.

Davies, B. M. A., and Yudkin, J. (1952) *Biochem. J.* **52**, 407.

Davies, H. E. F., Evans, B., Rees, H. M. N. and Fourman, P. (1958) *Guy's Hosp. Rep.* **107**, 486.

—— and Wrong, O. (1957) *Lancet*, **2**, 625.

Dawson, J., Dempsey, E., Bartter, F., Leaf, A., and Albright, F. (1953) *Metabolism*, **2**, 225.

Dorman, P. J., Sullivan, W. J., and Pitts, R. F. (1954) *J. clin. Invest.* **33**, 82.

Dragsted, P. J., and Hjorth, N. (1956) *Danish med. Bull.* **3**, 177.

Eales, L., and Linder, G. C. (1956) *Quart. J. Med.* N.S. **25**, 539.

Engel, W. J. (1951) *J. Amer. med. Ass.* **145**, 288.

Engle, R. L., and Wallis, L. A. (1957) *Amer. J. Med.* **22**, 5.

Evans, B. M., MacIntyre, I., MacPherson, C. R., and Milne, M. D. (1957) *Clin. Sci.* **16**, 53.

Fanconi, G., and de Chastonay, E. (1950) *Helv. paediat. Acta*, (Beiheft) **5**, 5.

Farquharson, R. F., Salter, W. T., Tibbetts, D. M., and Aub, J. C. (1931) *J. clin. Invest.* **10**, 221.

Fishberg, A. M. (1954) *Hypertension and Nephritis*. London.
Fiske, C. H. (1921) *J. biol. Chem.* **49**, 171.
—— and Subbarow, Y. (1925) Ibid. **66**, 375.
Fitzgerald, M. G., and Fourman, P. (1955) *Lancet*, **2**, 848.
Foss, G. L., Perry, C. B., and Wood, F. J. Y. (1956) *Quart. J. Med.* N.S. **25**, 185.
Fourman, P., and McCance, R. A. (1955) *Lancet*, **1**, 329.
Frick, P. G., Rubini, M. E., and Meroney, W. H. (1958) *Amer. J. Med.* **25**, 590.
Galan, E. (1955) *Rev. cubana Pediat.* **27**, 199.
Gamble, J. L., Blackfan, K. D., and Hamilton, B. (1925) *J. clin. Invest.* **1**, 359.
Giovannetti, S., and Bigalli, A. (1956) *Minerva nefrol.* (*Torino*) **3**, 84.
Harrison, H. E. (1954) *Pediatrics*, **14**, 285.
—— and Harrison, H. C. (1955) *J. clin. Invest.* **34**, 1662.
Hartman, A. C., and Darrow, D. C. (1928) Ibid. **6**, 127.
Henderson, L. J., and Palmer, W. W. (1915) *J. biol. Chem.* **21**, 37.
Hooft, C., and Vermassen, A. (1958) *Ann. paediat.* (*Basel*) **90**, 1.
Hunt, J. N. (1956) *Clin. Sci.* **15**, 119.
Jackson, W. P. U., and Linder, G. C. (1953) *Quart. J. Med.* N.S. **22**, 133.
Jaksch, R. von (1888) *Z. klin. Med.* **13**, 350.
Jurow, S. S., and Warthen, R. O. (1955) *Pediatrics*, **16**, 67.
Kaye, M. (1955) *J. clin. Invest.* **34**, 277.
Kyle, L. H., and Canary, J. H. (1956) *J. clin. Endocr.* **16**, 599.
Leaf, A. (1951) *New Engl. J. Med.* **245**, 504.
Lightwood, R., Payne, W. W., and Black, J. A. (1953) *Pediatrics*, **12**, 628.
Linder, G. C. (1927) *Quart. J. Med.* **20**, 285.
—— Bull, G. M., and Grayce, I. (1949) *Clin. Proc.* **8**, 1.
Lundbaek, K. (1951) *Lancet*, **2**, 419.
McCance, R. A., and von Finck, M. A. (1947) *Arch. Dis. Childh.* **22**, 200.
McCardle, B. (1955) *Biochem. J.* **60**, 647.
McCune, D. J., Mason, H. H., and Clarke, H. T. (1943) *Amer. J. Dis. Child.* **65**, 81.
Mahler, R. F., and Stanbury, S. W. (1956) *Quart. J. Med.* N.S. **25**, 21.
Merrill, J. P. (1955) *The Treatment of Renal Failure*. New York.
Milne, M. D. (1956) In *Lectures on the Scientific Basis of Medicine*, Vol. 5. London.
—— Muehrcke, R. C., and Aird, I. (1957) *Quart. J. Med.* N.S. **26**, 317.
—— —— and Heard, B. E. (1957) *Brit. med. Bull.* **13**, 15.
—— Stanbury, S. W., and Thomson, A. E. (1952) *Quart. J. Med.* N.S. **21**, 61.
Moller, E., McIntosh, J. F., and Van Slyke, D. D. (1929) *J. clin. Invest.* **6**, 427.
Oliveira, H. L. de (1953) *Metabolism*, **2**, 36.
Orloff, J., and Berliner, R. W. (1956) *J. clin. Invest.* **35**, 223.
Peters, J. P., and Van Slyke, D. D. (1931) *Quantitative Clinical Chemistry*. Baltimore.
Pines, K. L., and Mudge, G. H. (1951) *Amer. J. Med.* **11**, 302.
Pitts, H. H., Schulte, J. W., and Smith, D. R. (1955) *J. Urol.* (*Baltimore*) **73**, 208.
Pitts, R. F. (1953) *Harvey Lect.* **48**, 172.
—— Ayer, R. L., and Schiess, W. A. (1949) *J. clin. Invest.* **28**, 35.
—— Lotspeich, W. D., Schiess, W. A., and Ayer, R. L. (1948) Ibid. 27, 48.
Pratt, E. L., Geren, B. B., and Neuhauser, E. B. D. (1947) *J. Pediat.* **30**, 388.
Pyrah, L. N. (1958) *Proc. roy. Soc. Med.* **51**, 183.
Rector, F. C., Seldin, D. W., and Copenhaver, J. H. (1955) *J. clin. Invest.* **34**, 20.
Relman, A. S. (1954) *Amer. J. Med.* **17**, 435.
—— Etsten, B., and Schwartz, W. B. (1953) *J. clin. Invest.* **32**, 972.
—— and Schwartz, W. B. (1956) *New Engl. J. Med.* **255**, 195.
Reynolds, T. B. (1958) *Amer. J. Med.* **25**, 503.
Richterich-van Baerle, R., Goldstein, L., and Dearborn, E. H. (1956) *Nature* (*Lond.*) **177**, 698.
Roberts, K. E., Randall, H. T., Sanders, H. L., and Hood, M. (1955) *J. clin. Invest.* **34**, 666.
Robinson, J. R. (1954) *J. Physiol.* (*Lond.*) **124**, 1.
Roscoe, M. H. (1953) *J. clin. Path.* **6**, 201.

Rosenheim, M. L. (1956) In *Modern Views on the Secretion of Urine.*, London.
Salassa, R. M., Ulrich, J. A., and Hayes, A. B. (1954) *Proc. Mayo Clin.* **29**, 214.
Salvesen, H. A. (1928) *Acta med. scand.* **69**, 126.
Sanderson, P. H. (1952) *Biochem. J.* **52**, 502.
Sartorius, O. W., Roemmelt, J. C., and Pitts, R. F. (1949) *J. clin. Invest.* **28**, 423.
Saville, P. D., Nassim, R., Stevenson, F. H., Mulligan, L., and Carey, M. (1955) *J. Bone Jt Surg.* **37B**, 529.
Schreiner, G. E., Smith, L. H., and Kyle, L. H. (1953) *Amer. J. Med.* **15**, 122.
Schwartz, W. B., Jenson, R. L., and Relman, A. S. (1955) *J. clin. Invest.* **34**, 673.
—— and Relman, A. S. (1957) *New Engl. J. Med.* **256**, 1184.
Short, I. A. (1959) In preparation.
Sirota, J. H., and Hamerman, D. (1954) *Amer. J. Med.* **16**, 138.
Smith, L. H., and Schreiner, G. E. (1954) *J. Lab. clin. Med.* **43**, 347.
Stanbury, S. W. (1957 *a*) *Brit. med. Bull.* **13**, 57.
—— (1957 *b*) In *Advances in Internal Medicine*, Vol. 9. New York.
—— (1958) Unpublished observations.
—— and Macaulay, D. (1957) *Quart. J. Med.* N.S. **26**, 7.
—— and Thomson, A. E. (1952) *Clin. Sci.* **11**, 357.
Stapleton, T. (1956) Personal communication.
Tegelaers, W. H. H., and Tiddens, H. W. (1955) *Helv. paediat. Acta*, **10**, 269.
Van Slyke, D. D., and Cullen, G. E. (1917) *J. biol. Chem.* **30**, 289.
—— Linder, G. C., Hiller, A., Leiter, L., and McIntosh, J. F. (1926) *J. clin. Invest.* **2**, 255.
—— and Neill, J. M. (1924) *J. biol. Chem.* **61**, 523.
—— Philips, R. A., Hamilton, P. B., Archibald, R. M., Futcher, P. H., and Hiller, A. (1943) Ibid. **150**, 479.
Wilansky, D. L., and Schneiderman, C. (1957) *New Engl. J. Med.* **257**, 399.
Wolf, A. V. (1947) *Amer. J. Physiol.* **148**, 54.
Wood, F. J. Y. (1955) *Clin. Sci.* **14**, 81.
Wrong, O., and Gowenlock, A. H. (1959) In preparation.
Zweymuller, E., and Rossler, H. (1954) *Helv. paediat. Acta*, **9**, 28.

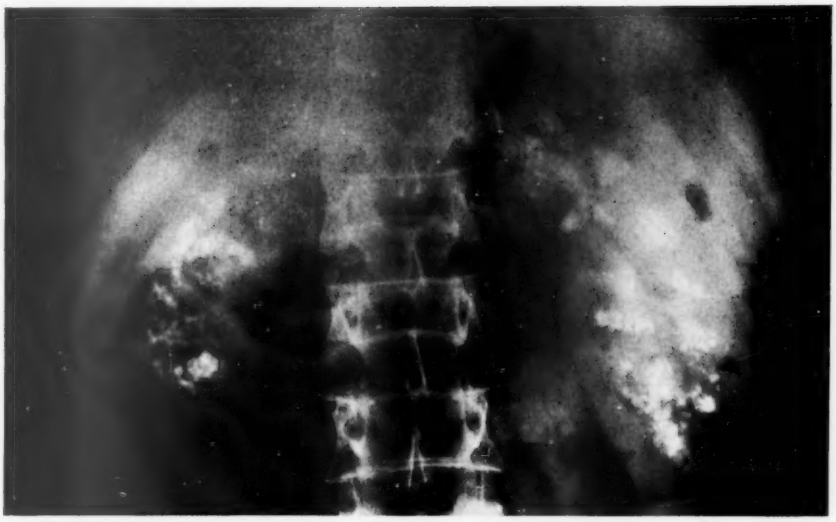


FIG. 17. Subject 30. Renal tubular acidosis

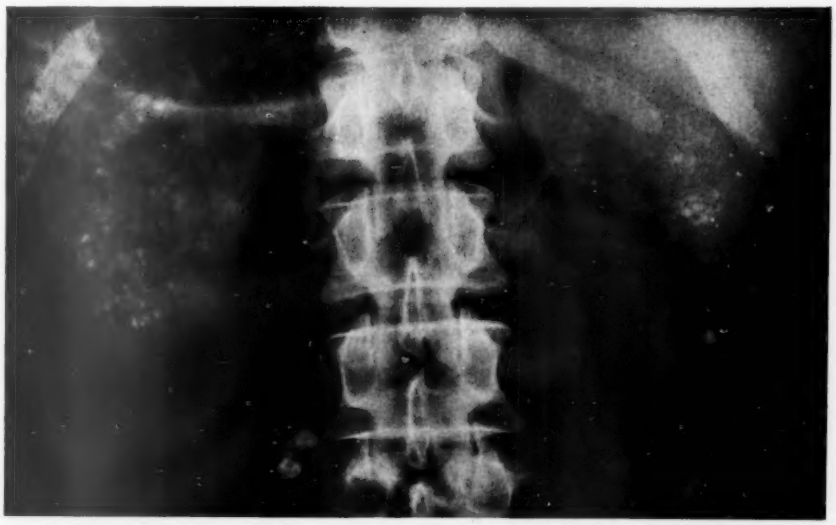


FIG. 18. Subject 38. Incomplete syndrome of renal tubular acidosis

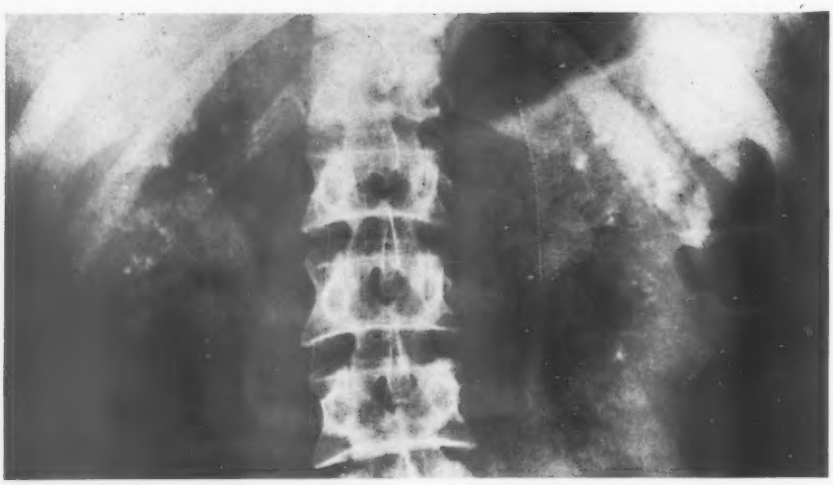


FIG. 19. Subject 39. Incomplete syndrome of renal tubular acidosis
(*By courtesy of Dr. A. R. Harrison*)

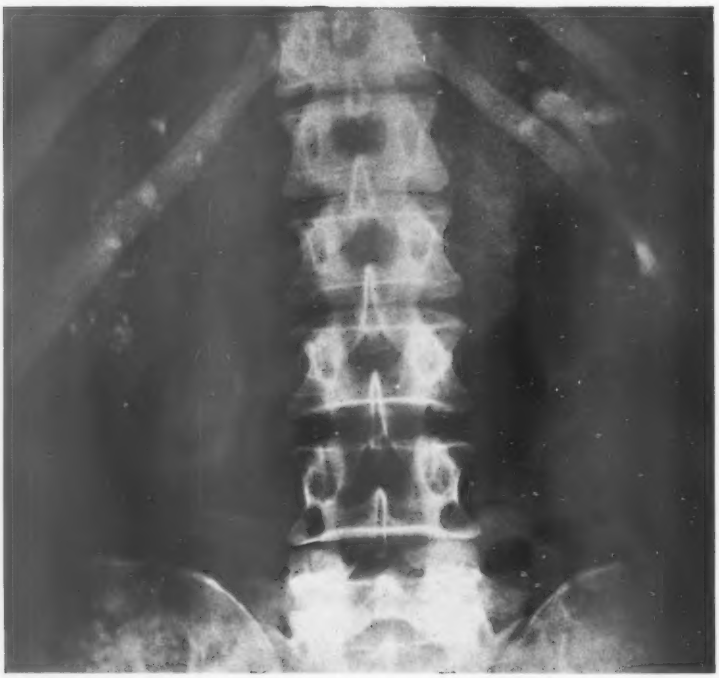
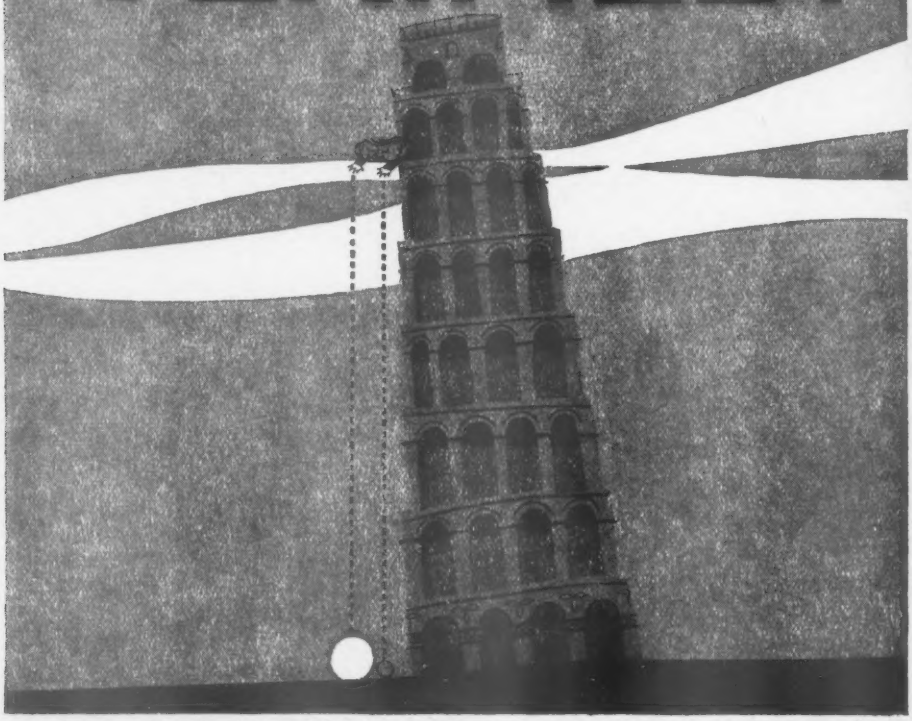


FIG. 20. Subject 40. Incomplete syndrome of renal tubular acidosis
(*By courtesy of Professor C. E. Dent*)

VERIFIED!



VASCULIT*

1-(4-hydroxyphenyl)-1-hydroxy-2-n-butylamino-ethane sulphate

GALILEO (1564–1642). The scene interpreted is Galileo's famous experiment from the Leaning Tower of Pisa. Here he afforded to students the ocular demonstration that bodies of different weights fall with the same velocities. In dynamics, his writings paved the way for Newton.

A great number of practitioners have now personally verified the Vasculit claims—commencing with the simple "cold hands and feet" test and following on with suitable cases of minor vasomotor dysfunctions. This and existing clinical evidence[1] clearly establishes Vasculit as an unusually safe and effective haemokinetic agent with an exceptionally wide range of application. It has been prescribed with marked benefit in the following conditions:

Vasomotor dysfunctions — "cold hands and feet"; acrocyanosis; chilblains.

Vascular diseases — Raynaud's disease; Buerger's disease; peripheral arteriosclerosis.

Local ischaemic lesions — gravitational leg ulcers; bedsores.

Contra-indication — recent myocardial infarction.

Haemokinesis is achieved by an improvement in cardiac efficiency, associated with an increase in the stroke volume and an opening up of the peripheral arterioles. There is no change in the heart rate and no significant alteration in blood pressure. Vasculit is an unusually safe drug.

1 *Dtsch. med. Wschr.* (*1953*), **78**, *1061*. *Wien. med. Wschr.* (*1951*), **101**, *544*. *Arch. orthop.Unfall-Chir.* (*1956*), **48**, *209*. *Wien. klin. Wschr.* (*1954*), **66**, *743*. *Hautarzt.* (*1953*), **4**, *78*.

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